Optimising clinical trials in acute myocardial infarction complicated by cardiogenic shock: a statement from the 2020 Critical Care Clinical Trialists Workshop

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Acute myocardial infarction complicated by cardiogenic shock (AMICS) is a critical syndrome with a high risk of morbidity and mortality. Current management consists of coronary revascularisation, vasoactive drugs, and circulatory and ventilatory support, which are tailored to patients mainly on the basis of clinicians' experience rather than evidence-based recommendations. For many therapeutic interventions in AMICS, randomised clinical trials have not shown a meaningful survival benefit, and a disproportionately high rate of neutral and negative results has been reported. In this context, an accurate definition of the AMICS syndrome for appropriate patient selection and optimisation of study design are warranted to achieve meaningful results and pave the way for new, evidence-based therapeutic options. In this Position Paper, we provide a statement of priorities and recommendations agreed by a multidisciplinary group of experts at the Critical Care Clinical Trialists Workshop in February, 2020, for the optimisation and harmonisation of clinical trials in AMICS. Implementation of proposed criteria to define the AMICS population—moving beyond a cardio-centric definition to that of a systemic disease—and steps to improve the design of clinical trials could lead to improved outcomes for patients with this life-threatening syndrome.

Introduction

Cardiogenic shock is a life-threatening syndrome that involves peripheral hypoperfusion and organ dysfunction due to primary cardiac dysfunction.[1] Several acute and chronic underlying cardiac conditions can induce cardiogenic shock, the most frequent being acute myocardial infarction (AMI). AMI complicated by cardiogenic shock (AMICS) occurs in fewer than 5% of AMI cases, with a high proportion of those having out-of-hospital cardiac arrest. Patients who present with or develop AMICS still have relevant morbidity and mortality rates of more than 50% after 1 year.[2,3]

The management of AMICS frequently includes coronary revascularisation, vasoactive drugs, and circulatory and ventilatory support, administered largely according to clinicians' experience rather than evidence-based recommendations. Indeed, for many therapeutic interventions in this setting, few adequately designed randomised clinical trials (RCTs) have shown a clinically meaningful benefit in the management of AMICS. Although we acknowledge that some interventions might simply be ineffective, other factors such as study design and patient selection have probably affected the results of some trials. A disproportionately high rate of neutral and negative results is reported for phase 3 RCTs in critically ill patients, despite promising phase 2 studies. As a consequence, although the number of RCTs is growing, few advances in the treatment of AMICS have been achieved in the past three decades, and patient outcomes remain poor.[3] In this context, an accurate definition of the AMICS syndrome for appropriate patient selection and optimisation of study design are warranted to increase the possibility of identifying novel, evidence-based therapeutic options.

On Feb 26, 2020, during the second Critical Care Clinical Trialists (3CT) Workshop in Washington DC (USA), a group of experts convened to discuss, debate, and reflect on approaches to optimise trials in cardiogenic shock, with the aim of providing 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 USA and the EU, federal grant managers, and industry representatives. Workshop presentations were given, followed by detailed discussions,

Key messages

- Few advances in the treatment of AMICS have been made in the past 30 years; there is an unmet need for adequately designed randomised clinical trials
- Optimal definition of AMICS, patient selection, and study design are required to achieve clinically meaningful results and new evidence-based treatments
- AMICS is a systemic disease characterised by peripheral hypoperfusion and organ dysfunction, resulting from acute myocardial infarction; the definition of AMICS should consider the systemic pathophysiology of shock
- Accurate description of AMICS severity, evolution, and mechanisms of disease are crucial to reduce heterogeneity and identify the population most likely to benefit from a tested treatment
- Alternative study designs, tailored to different clinical scenarios, might provide valuable insights into treatment effects

AMICS=acute myocardial infarction complicated by cardiogenic shock.

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on a range of topics pertaining to trial design. In this Position Paper, we present consensus views of this expert group on the steps required to optimise the design of clinical trials of therapeutic options for AMICS, including improved criteria to define the AMICS population.

Development of recommendations

The focus of the meeting and priority areas for discussion were proposed by the workshop director (AM). Invited participants were assigned to one or more topics before the meeting, according to their field of expertise. Participants provided a short presentation, a written abstract, and the relevant literature related to their topic(s). Each topic was then discussed among workshop participants who were developing recommendations for the optimisation of clinical trials in AMICS, and consensus was achieved on the relevant messages to be included in the manuscript. If there were any areas of uncertainty or controversy, the topic was discussed until a consensus was reached. The literature searches were updated and the agreed views finalised as the Position Paper was written and revised.

Improved definition of the AMICS population

Current definitions of AMICS and their limitations

AMICS is defined as a state in which inadequate cardiac output caused by an AMI—with or without ST elevation on electrocardiogram—results in peripheral hypoperfusion.[2,4] Clinical and biochemical manifestations of AMICS often include persistent arterial hypotension despite correction of hypovolaemia, cold and clammy skin, oliguria, altered mental state, and elevated serum lactate concentrations. Although there is broad agreement on this pragmatic clinical definition, the translation of these features into defined inclusion and exclusion criteria for use in clinical trials is more challenging.

A recent definition of cardiogenic shock by the Acute Cardiovascular Care Association of the European Society of Cardiology includes four criteria: presence of hypotension, evidence of hypoperfusion, evidence of elevated left ventricular filling pressures, and a cardiac cause of shock.[5] Completed and ongoing trials have used somewhat different criteria to define shock in the presence of AMI (table),[6–10] but there have been no substantial changes in the definition over the past 20 years. For the definition of shock, most studies have required the combination of arterial hypotension (systolic blood pressure <90 mm Hg or the need for vasoactive drugs or inotropes to maintain systolic blood pressure at ≥90 mm Hg) and evidence of end-organ hypoperfusion, based on ill-defined or arbitrary clinical and biochemical criteria, such as cool extremities, altered mental status, urine output of less than 30 mL/h, or elevated serum lactate concentrations. Of note, some studies did not require evidence of hypoperfusion for the definition of shock, but instead used other criteria that reflect illness severity such as the need for mechanical ventilation. Considerable heterogeneity across studies was found regarding the use of cardiac imaging and right heart catheterisation for the definition of the cardiac origin of shock (table).

Furthermore, for patients who present with myocardial infarction and signs of peripheral hypoperfusion, determining the contribution of myocardial ischaemia to the development of shock can be challenging. Indeed, several conditions other than acute left ventricular ischaemic dysfunction might lead to shock. In the SHOCK trial registry, a quarter of included patients had causes of shock other than acute left ventricular dysfunction, such as right heart failure, valvular disease, mechanical complications of myocardial infarction, or pericardial tamponade.[11] A selection of clinical conditions leading to hypoperfusion in the presence of clinical, biochemical, and electrocardiographic features of myocardial infarction is presented in panel 1.

The AMICS population is heterogeneous, with clinical presentations ranging from normotensive shock (ie, signs of hypoperfusion without hypotension)[12] to profound hypotension, and from mild hypoperfusion to refractory shock (ie, persisting hypoperfusion despite the administration of volume, inotropes, and vasoconstrictors). Some studies have included patients with out-of-hospital cardiac arrest and pulseless states, whereas others have included patients at risk of developing cardiogenic shock (the so-called pre-shock state). Notably, AMICS is present at hospital admission in only about half of patients who develop the syndrome, whereas the other half develops the condition during their hospital stay (mostly during the first hours after admission).[13]

Thus, a major challenge in conducting and interpreting the results of trials in the AMICS population relates to the lack of a precise, global definition of the syndrome and the absence of a widely accepted framework describing the clinical presentation, severity, and conditions leading to shock.

Hypoperfusion and organ dysfunction in the definition of AMICS

It is increasingly apparent that cardiogenic shock is a systemic disease characterised by peripheral hypoperfusion and involving several organ systems. In the case of AMI, cardiac contractile dysfunction related to myocardial ischaemia, inflammation, and other mechanisms acts as a trigger, inducing many extra-cardiac alterations, including peripheral hypoperfusion, activation of damage-associated molecular patterns, inflammation, multiorgan failure, and death. Although included in most definitions of cardiogenic shock, hypotension is not a mandatory criterion, and although hypotension can accompany hypoperfusion, normotensive cardiogenic shock can occur in early-stage disease.[12,14]

Increased blood lactate concentrations have long been recognised to occur in circulatory shock[15] and are associated with disease severity and mortality.[16] Associations between cardiogenic shock, organ dysfunction, and outcomes (eg,

	Year or trial status	Hypotension criteria	Hypoperfusion criteria	Haemodynamic criteria	Echocardiographic criteria	Additional criteria	Number of patients	Intervention	Primary endpoint
SHOCK[6]	1999	SBP <90 mm Hg or medical support	Cold extremities or urine output <30 mL/h	Cardiac index ≤2·2 L/min per m² and PAWP ≥15 mm Hg	..	..	302	Emergency revascularisation *vs* initial medical stabilisation	All-cause death at 30 days
IABP-SHOCK II[7]	2012	SBP <90 mm Hg or medical support	Altered mental state, cold skin, urine output <30 mL/h, or serum lactate >2·0 mmol/L	..	..	..	600	Intra-aortic balloon pump *vs* no intra-aortic balloon support	All-cause death at 30 days
CULPRIT-SHOCK[8]	2017	SBP <90 mm Hg or medical support	Altered mental state, cold skin, urine output <30 mL/h, or serum lactate >2·0 mmol/L	..	..	..	686	Culprit lesion-only PCI *vs* multivessel PCI	All-cause death or severe renal failure at 30 days
IMPRESS[9]	2017	SBP <90 mm Hg or medical support	..	..	..	Mechanical ventilation	48	Percutaneous mechanical circulatory support *vs* intra-aortic balloon pump	All-cause death at 30 days
OPTIMACC[10]	2018	SBP <90 mm Hg, MAP <65 mm Hg, or medical support	..	Cardiac index ≤2·2 L/min per m² and PAWP ≥15 mm Hg	LVEF <40%	..	57	Epinephrine *vs* norepinephrine	Change in cardiac index at 3 days
EUROSHOCK (NCT03813134)	Ongoing	SBP <90 mm Hg or medical support	Altered mental state, cold skin, urine output <30 mL/h, or serum lactate >2·0 mmol/L	..	..	Pulmonary congestion	~428	Immediate PCI plus medical therapy plus early VA-ECMO *vs* immediate PCI plus medical therapy	All-cause death at 30 days
ECLS-SHOCK (NCT03637205)	Ongoing	SBP <90 mm Hg or medical support	Altered mental state, cold skin, urine output <30 mL/h, or serum lactate >3·0 mmol/L	..	..	..	~420	PCI (or CABG) plus medical treatment plus ECLS (VA-ECMO, see above) *vs* PCI (or CABG) plus medical treatment	All-cause death at 30 days
ANCHOR (NCT04184635)	Ongoing	SBP <90 mm Hg or medical support	Altered mental state, cold skin, urine output <30 mL/h, or serum lactate >2·0 mmol/L	..	..	Pulmonary congestion	~400	VA-ECMO plus intra-aortic balloon pump *vs* standard treatment	All-cause death or rescue ECMO at 30 days

We selected three of the largest trials (SHOCK, IABP-SHOCK II, and CULPRIT-SHOCK), two contemporary trials (IMPRESS and OPTIMACC, a trial of pharmacological treatment), and three ongoing trials. AMICS=acute myocardial infarction complicated by cardiogenic shock. CABG=coronary artery bypass graft. ECLS=extracorporeal life support. ECMO=extracorporeal membrane oxygenation. LVEF=left ventricular ejection fraction. MAP=mean arterial pressure. PAWP=pulmonary artery wedge pressure. PCI=percutaneous coronary intervention. SBP=systolic blood pressure. VA-ECMO=venoarterial ECMO.

Table: **Definitions of shock and primary endpoints in clinical trials of AMICS**

mortality, organ dysfunction) have also been reported.[17,18] These links with outcomes might be related to the severity of tissue hypoperfusion and systemic congestion or, in patients with cardiac arrest, might be aggravated by the use of vasoactive agents, the low-flow state observed during cardiopulmonary resuscitation, or detrimental effects of the injured brain.[10,19]

We therefore propose to move beyond a cardio-centric definition of AMICS to that of a systemic disease characterised by peripheral hypoperfusion and organ dysfunction resulting from AMI. The proposed steps to confirm the diagnosis of AMICS and its severity are summarised in figure 1.[20]

Role of imaging in the definition of AMICS

The ischaemic precipitant of cardiogenic shock is recognised and classified according to the Fourth Universal Definition of Myocardial Infarction, based on symptoms, electrocardiography, and cardiac troponin values[21] and confirmed with coronary angiography or, rarely, other imaging modalities, such a coronary CT. This diagnostic approach might be appropriate for certain patients (such as those with isolated de-novo ST-elevation myocardial infarction); however, cardiogenic shock is not always due to acute left ventricular myocardial disease or dysfunction (panel 1), and diagnosis of cases with other causes might require an alternative approach.

Panel 1: **Selection of clinical conditions leading to hypoperfusion in the presence of myocardial infarction**

- Large AMI with acute left ventricular dysfunction (typical case)
- AMI with acute valvular or mechanical complication
- AMI with right ventricular involvement
- AMI with severe bradycardia, high-degree atrioventricular block, or tachyarrhythmias
- Small AMI in the context of pre-existing severe cardiac dysfunction (eg, heart failure with reduced ejection fraction)
- AMI in severe, diffuse coronary artery disease (unknown culprit lesion)
- Type 2 AMI with non-occlusive coronary arteries
- AMI with iatrogenic adverse effects (eg, related to excessive diuretics, β blockers)

AMI=acute myocardial infarction.

The systematic use of echocardiography in cardiogenic shock is recommended in several guidelines,[4,22,23] and we advocate its use in clinical studies of cardiogenic shock. Cardiac imaging, such as echocardiography, is essential in AMICS to confirm the cardiac cause of shock (ie, left or right ventricular dysfunction, previous or concomitant structural heart disease, or mechanical complications), and it helps to determine the culprit lesion in cases of multivessel coronary artery disease when electrocardiography is not informative. Data derived from cardiac imaging can be used to guide medical treatment and allow improved phenotypic characterisation of patients included in studies. Furthermore, the combination of imaging modalities might provide valuable insights into the underlying mechanisms of cardiogenic shock, and enable the distinction between pre-existing and infarction-induced, new-onset cardiac dysfunction.

Assessment of AMICS severity

Current approaches to severity assessment

The Killip classification for mortality risk in AMI is insufficiently granular to provide a meaningful framework for current use, particularly in the era of mechanical circulatory support (MCS).[24] Several clinical scores exist to quantify the severity of cardiogenic shock and predict short-term survival,[16,25,26] but most have not been prospectively evaluated and there is no consensus on their use in clinical practice. The Society for Cardiovascular Angiography and Interventions (SCAI) proposed a new classification system for the severity of cardiogenic shock, endorsed by the American College of Cardiology, the American Heart Association, the Society of Critical Care Medicine, and the Society of Thoracic Surgeons.[20] The SCAI shock classification system consists of five severity stages (figure 1).

This SCAI classification system was based on expert consensus and was applied in three large cohorts.[27–29] Jentzer and colleagues showed that SCAI classification was correlated with in-hospital mortality,[27] and that the association with mortality continued after hospital discharge.[28] Two other large studies showed similar results.[29,30] In the first prospective evaluation of the SCAI shock stages, Baran and colleagues reported the outcomes of 166 patients in whom SCAI shock stage was assessed by a multidisciplinary shock team at presentation and 24 h later.[31] They confirmed a significant correlation between initial shock stage and 30-day survival. Reassessment at 24 h was also predictive of outcome: patients who improved by one or more SCAI stages had a markedly better survival than those with no change or a deterioration in SCAI stage.[31]

The SCAI classification of cardiogenic shock severity is not only clinically relevant, but might also support research by reducing the heterogeneity of patients included in cardiogenic shock trials. In addition, it could be used to define the response to any intervention (ie, deterioration, stabilisation, or improvement). Furthermore, this classification system considers not only the clinical picture at hospital admission, but also its evolution after admission, thereby reducing the risk of missing or misclassifying patients who develop cardiogenic shock during their hospital stay.

We advocate the addition of organ function assessment (normal *vs* altered; figure 1) to the original SCAI classification system[20] because this might help to refine discrimination of shock stages B (no new organ dysfunction), C (new dysfunction of at least one organ), and D or E (multiorgan failure).

Future directions to improve diagnosis and severity assessment

Established cardiovascular biomarkers reflect the severity of cardiac dysfunction but have been shown to provide insufficient diagnostic and predictive value in cardiogenic shock.[16,32,33] Four circulating proteins—liver-type fatty acid-binding protein, β2 microglobulin, fructose-bisphosphate aldolase B, and SerpinG1, which reflect kidney, liver, and bowel injury, systemic inflammation, and immune activation—have been identified to discriminate risk of cardiogenic shock and included in the Cardiogenic Shock 4 proteins (CS4P) score, a new patient risk score to predict short-term mortality in AMICS.[34] An improvement in risk prediction was achieved with reclassification of patients using the CS4P score when compared with other contemporary risk scores. Two other circulating biomarkers, bio-adrenomedullin and dipeptidyl-peptidase 3, have been shown to have strong prognostic value for cardiogenic shock and, more importantly, to be biologically active and act as targets for antibodies that have been shown to improve outcomes in preclinical studies.[33,35–37] However, the results need to be verified in multicentre studies; moreover, none of these parameters is currently available for use in clinical practice.

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Novel biomarkers are needed to improve understanding of the pathophysiology of AMICS and increase the accuracy of diagnosis and risk stratification.[38] Developments in the biological sciences and the study of omics (ie, genomics, transcriptomics, proteomics, and metabolomics) have enabled identification of novel biomarkers reflecting the systemic effects of cardiogenic shock (organ dysfunction and inflammation), which might help to better define patient phenotypes.[39]

The wave of new biomarker candidates promises to aid clinical decision making and patient stratification in cardiogenic shock. Moreover, interpretation using artificial intelligence (eg, with machine learning) might further increase understanding of the pathophysiology of AMICS, which could, in turn, lead to improvements in diagnostic and prognostic accuracy, and allow personalisation of treatment. In particular, refined stratification of patients with AMICS might help to guide clinicians in identifying patients who are declining or at risk of decline, and in selecting high-risk patients for more invasive procedures, including MCS. Furthermore, the biological effects of some novel biomarkers could be modulated to improve outcomes in trials that use biomarker-guided patient selection.[40]

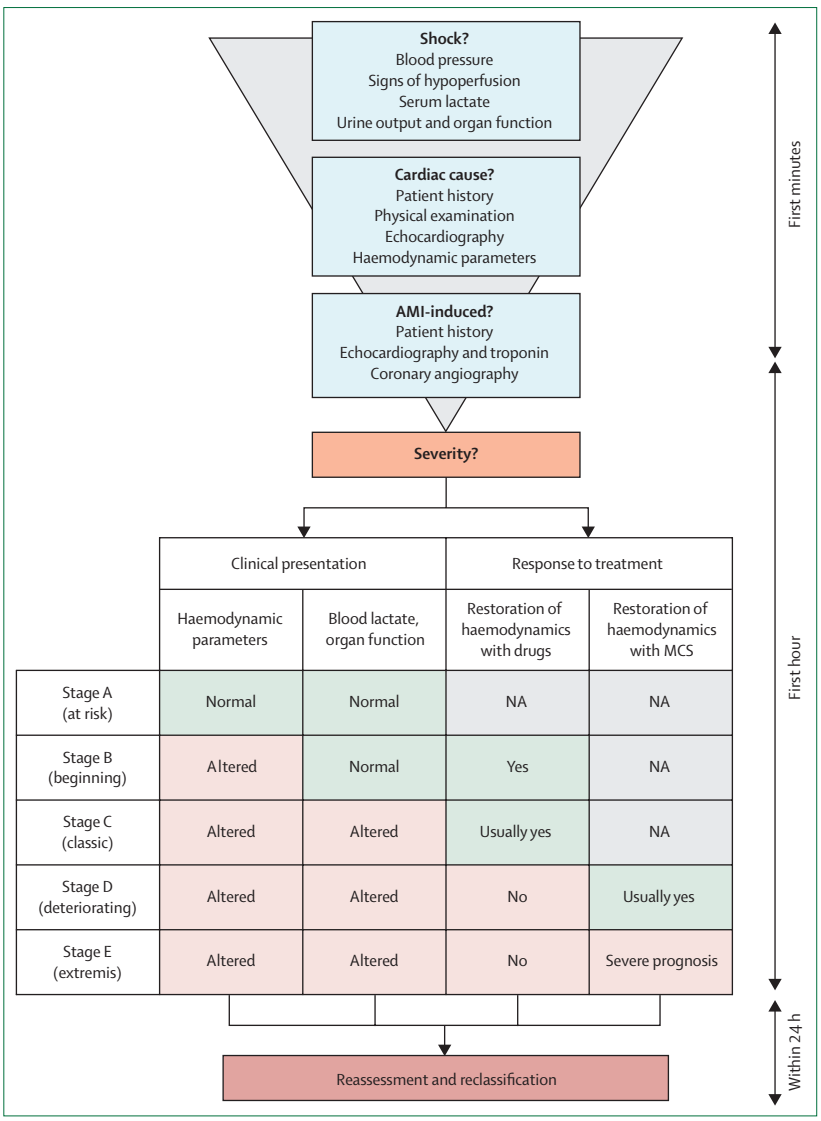
Trial design for cardiogenic shock

General considerations

When designing clinical trials, the definition of the study population is of major importance in demonstrating a meaningful effect of a therapeutic intervention for a specific clinical condition. This step is particularly important for studies of clinical syndromes, such as cardiogenic shock, rather than specific diseases. Syndromes are often heterogeneous in terms of underlying disorder and severity of clinical presentation, which can increase noise in the data and might mask a beneficial effect of the treatment being tested. The use of a global definition of cardiogenic shock and the adoption of a common shared framework to phenotype patients and define severity are therefore needed to improve the design of future studies.

Selection of AMICS severity for trials

The study population should include the largest proportion of patients likely to benefit from a therapeutic intervention (figure 2).[41] For example, when designing a trial to test MCS for AMICS, researchers should consider two key principles: first, 50–60% of all patients with AMICS will survive without a device[3] (figure 2, cohort X); and second, if all patients are implanted with an MCS device, deaths related to complications of implantation may occur. These patients in cohort X probably do not need an MCS device. Other patients do not need an MCS device because they are too sick or have conditions that cannot be improved by a device (eg, hypoxic brain injury after out-of-hospital cardiac arrest; figure 2, cohort Z). Initial patient stratification to predict the potential response to treatment is challenging but crucial to identify patients who are most likely to benefit from a therapeutic intervention (figure 2, cohort Y)—ie, patients who are neither too healthy (for whom the risk of potential



	Clinical presentation		Response to treatment	
	Haemodynamic parameters	Blood lactate, organ function	Restoration of haemodynamics with drugs	Restoration of haemodynamics with MCS
Stage A (at risk)	Normal	Normal	NA	NA
Stage B (beginning)	Altered	Normal	Yes	NA
Stage C (classic)	Altered	Altered	Usually yes	NA
Stage D (deteriorating)	Altered	Altered	No	Usually yes
Stage E (extremis)	Altered	Altered	No	Severe prognosis

Figure 1: **Diagnosis and severity assessment of AMICS**
The upper part of the figure outlines steps proposed by participants of the Critical Care Clinical Trialists Workshop to confirm the diagnosis of AMICS, moving towards a systemic definition of disease characterised by peripheral hypoperfusion and organ dysfunction resulting from AMI. Echocardiographic and haemodynamic data should be collected as soon as possible (within minutes to a few hours of presentation) to confirm a cardiac cause of shock without delaying revascularisation. The lower part of the figure summarises the stages of AMICS severity based on the Society for Cardiovascular Angiography and Interventions shock classification system,[20] with the addition of organ function assessment. Stage A includes patients who are haemodynamically stable but who have acute cardiovascular disease that puts them at risk of developing cardiogenic shock. Stage B includes patients who are starting to show signs of haemodynamic instability, including hypotension or tachycardia, but who do not have signs of hypoperfusion or organ dysfunction. Stage C defines patients who have cardiogenic shock characterised by hypoperfusion without deterioration, and new dysfunction of at least one organ. Stage D refers to patients with cardiogenic shock and multiorgan failure whose haemodynamic instability or hypoperfusion worsens and who do not respond to initial medical interventions. Stage E defines patients with cardiogenic shock despite multiple interventions, including MCS. AMI=acute myocardial infarction. AMICS=AMI complicated by cardiogenic shock. MCS=mechanical circulatory support. NA=not applicable.

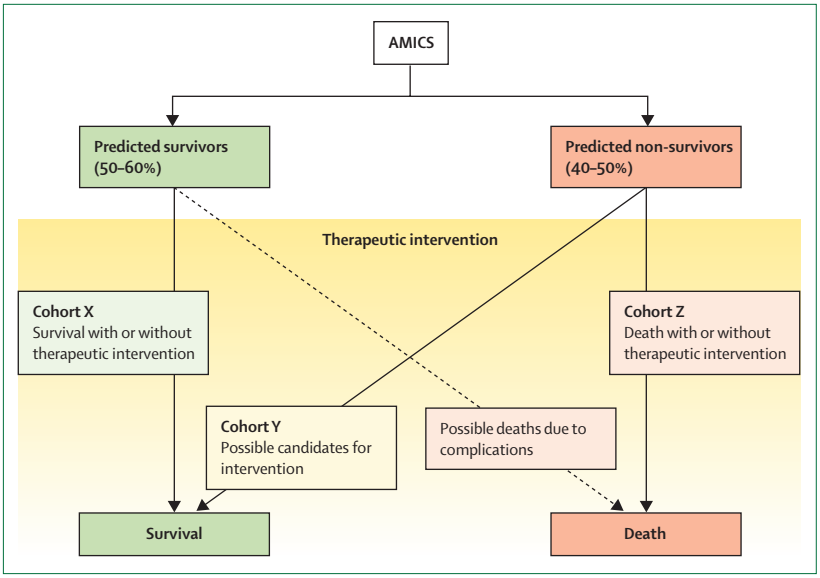


Figure 2: **Contemporary risk stratification for the definition of study populations in AMICS**
When studying a therapeutic intervention aimed at improving survival in a clinical condition characterised by high mortality, some patients are likely to survive (predicted survivors) and other patients are likely to die (predicted non-survivors). If a therapeutic intervention is given to the group of predicted survivors, most of them will survive regardless of the intervention (cohort X) and some (few) will have treatment-related adverse events leading to death. By contrast, if a therapeutic intervention is given to the group of predicted non-survivors, some of them will die independently of the treatment (cohort Z), often as a result of other conditions that cannot be improved by the therapeutic intervention. Therefore, a trial of a therapeutic intervention in cohort X or Z is unlikely to demonstrate a clinically meaningful benefit. If a study enrols patients who are expected to die but might benefit from the studied treatment (cohort Y), the effect of the therapeutic intervention can be adequately tested. AMICS=acute myocardial infarction complicated by cardiogenic shock. Modified from Thiele and colleagues.[41]

complications of the investigated therapy outweigh the potential benefit) nor too sick (for whom treatment might be futile).

Blood pressure and lactate concentrations are currently used as key inclusion criteria in RCTs in AMICS; assessment of the incremental value of additional clinical, haemodynamic, and biochemical parameters that might improve enrichment of patients with cardiogenic shock is advisable. The effects of interventions in AMICS will probably also depend on disease severity at the time of treatment. We propose that future trial design combines additional criteria with blood pressure and lactate concentrations in a comprehensive classification to stratify patients prospectively. Assessment with the SCAI shock classification at the time of enrolment and 24 h later could also help to capture rapid improvement or late deterioration to determine the need for treatment escalation or de-escalation. Finally, the most severe AMICS cases (eg, SCAI stage E) with the highest risk of death should not be included routinely in trials, to reduce data noise, but should be reported in registries or in dedicated studies.

Role of cardiac imaging in AMICS trials

One in four patients included in the SHOCK trial registry had causes of shock other than acute left ventricular dysfunction (panel 1),[11] with relevant implications for treatment. Echocardiography should be performed routinely in all patients with AMICS to identify the cardiac mechanisms involved and guide treatment. Images should be acquired as soon as possible without delaying revascularisation. Therefore, imaging findings should be part of the definition of AMICS and a mandatory inclusion criterion for studies to define a more homogeneous population. The minimal echocardiographic examination should include a quantitative assessment of left and right ventricular size and function, and a semi-quantitative assessment of valve disease, and should determine the presence of pericardial tamponade or mechanical complications (eg, ventricular septal defect, free wall rupture).[42] Finally, serial examinations could be evaluated as surrogate endpoints to determine improvement (at least a mechanistic effect) in cardiac function induced by the tested therapeutic intervention without clinical translation to improved mortality.

Trials with drugs or devices

Several differences exist between trials of drugs and those of devices, some of which might be independent of the clinical context and related to regulatory or organisational factors. First, the journey from discovery to approval and clinical use differs for a drug and a device, mainly owing to regulatory issues. In the EU, the approval of a drug requires at least one large phase 3 RCT showing a clinically meaningful and significant benefit, usually for mortality, whereas a device can be introduced into clinical practice after obtaining the CE mark—a certificate of compliance with EU directives on performance, quality, safety, and efficacy of the product—without the need for a clinical trial. Second, whereas the delivery of a study drug (or placebo) can be standardised and monitored, a device trial has many more confounding factors related to the device, its optimal use, settings, and staff experience. Third, double-blind or placebo-controlled studies of devices (eg, sham procedures) are challenging or impossible to conduct. Fourth, the net effect of therapeutic intervention is the difference between its beneficial effects and adverse events; the proportions of those who survive with or without the intervention, those who die independently of the intervention, and those who benefit from the intervention largely depend on the severity of AMICS and the characteristics of the therapeutic intervention. In particular, the potential adverse events of a therapeutic intervention need to be considered when defining the study population.[43] Whereas patients in AMICS stages D or E with extremely high mortality rates could be enrolled in trials investigating more risky treatments such as the implantation of devices, patients with AMICS stages A or B should be excluded to avoid unnecessary treatment-related complications.

Control arm in AMICS trials

In general, patients randomly assigned to the control group of an RCT should be optimally treated according

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to the best available recommendations, in addition to receiving a placebo or a sham treatment instead of the investigated drug or device, if possible. Design of the control arm is easily achieved when the established standard-of-care treatment consists of no drugs or only symptom-relieving drugs (in this case, patients in the control group receive placebo or sham treatment only) or when the standard treatment includes established evidence-based measures. The situation is more complicated for AMICS because few data from RCTs to define standard treatment exist and there is substantial equipoise (ie, genuine uncertainty about whether a treatment will be beneficial). The SHOCK[6] and CULPRIT-SHOCK[8] trials showed that an early invasive strategy with coronary revascularisation restricted to the culprit lesion is beneficial, and the IABP-SHOCK II[7] trial showed that routine use of an intra-aortic balloon pump does not confer a significant benefit. Beyond that, few data exist to support the use of inotropes, vasopressors, volume resuscitation, mechanical ventilation, pacing, or MCS. Thus, standard treatment is determined largely by expert recommendations and should be carefully described in RCT protocols, with as much detail as possible to reduce bias owing to heterogeneity in ancillary treatments (eg, medical treatments, mechanical ventilation, additional devices). Sufficient resources should be allocated to the education of the study teams to minimise deviations from the protocol in each group. The implementation of standardised team-based care for cardiogenic shock might also have a beneficial effect on outcomes in the control arm.[44] Notably, if the investigated treatment is already part of the standard treatment of a potential investigating centre, that centre is unlikely to recruit and randomly assign patients to a control arm without that study intervention. Therefore, careful centre selection and continuous education are crucial to ensure optimal enrolment and reduce selection bias.

The study protocol should also include a detailed description of the escalation strategy and the measures to minimise crossovers in both treatment and control arms. For example, when investigating the effect of MCS, the possibility of escalation to MCS should also be offered to patients randomly assigned to the control group, defined a priori and, if possible, by use of devices other than the study device to minimise crossovers. In such cases, the results should include the per-protocol (or as-treated) analyses in addition to the intention-to-treat analysis. A comparison of baseline characteristics of patients who crossed over with those who did not might provide valuable insights. Finally, when investigating drugs or devices that require particular expertise available only in high-volume centres, bias related to transfer to the hub centre should be minimised. For example, if patients are transferred for device implantation from a spoke centre to the hub, and the control group is treated in spoke centres only, the treatment effect might be attributable to differences in the treating institutions rather than the treatment itself.[45]

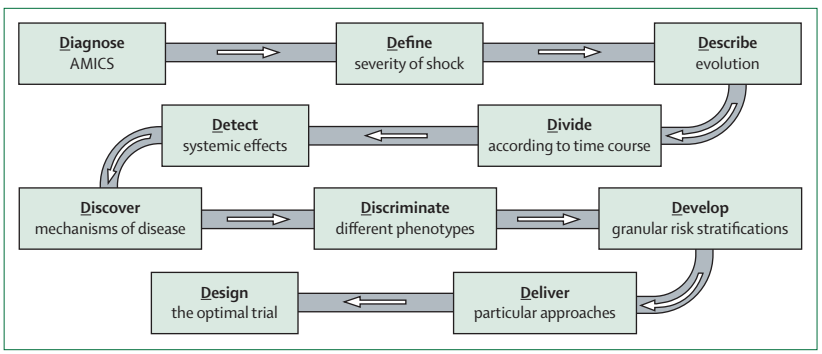

Figure 3: **The road towards optimal AMICS trial design**
The D-road towards optimal trial design in AMICS includes ten steps. AMICS should be diagnosed according to a global definition (ie, haemodynamic derangements, systemic hypoperfusion, and evidence of acute myocardial ischaemic cause; figure 1). The severity of shock should be defined (figure 1) and its evolution (improvement *vs* deterioration) during the first hours of conventional treatment described. Patients presenting with AMICS and those who develop shock during their hospital stay should be divided, if possible. Systemic effects of AMICS (eg, inflammation, organ dysfunction) should be detected, and discovery of underlying pathophysiological mechanisms is essential to identify patients who might respond to particular interventions. The discrimination of different phenotypes of AMICS on the basis of advanced haemodynamics, imaging techniques, and biomarkers might enable the development of more granular risk stratification. Furthermore, particular approaches for different scenarios (eg, prehospital setting, catheterisation laboratory, intensive care unit, drug *vs* device study) should be delivered. Finally, methodological issues (eg, granular endpoints, statistical models, and study protocol) should be considered when designing the optimal trial. AMICS=acute myocardial infarction complicated by cardiogenic shock.

Trial endpoints, sample size, and power

Cardiogenic shock trials aim to demonstrate improved survival and reduced morbidity. The sample size of an RCT will ideally support the estimation of a precise average (or overall) treatment effect (ie, comparison of the study arms), in addition to assessments of heterogeneity of treatment effect (ie, comparisons by disease severity or among clinically relevant subgroups). Because large sample sizes are particularly challenging in the context of AMICS (owing to long recruiting periods, expansion to low-volume or low-expertise centres, and high costs), other options to increase power with smaller sample sizes should be considered. The primary options to achieve lower sample sizes include the use of advanced statistical models to examine the data, such as longitudinal models (which might be subject to criticism due to complexity in interpretation) or more granular composite endpoints. We propose three alternative continuous (as opposed to binary) hierarchical composite endpoints for the cardiogenic shock community to consider in future trials: alive and organ-support free, global rank score, and days alive and out of hospital. These three approaches to efficacy measurement could capture important outcomes in cardiogenic shock trials, while also increasing statistical power due to their continuous nature.

The combined endpoint of alive and organ-support free can be straightforwardly reported using the so-called win ratio. This method compares all study participants from

Panel 2: Special considerations applicable to different clinical scenarios in AMICS

Prehospital setting
- Few data exist on treatment delivered before hospital admission
- Prehospital treatment initiation might affect outcomes

Out-of-hospital cardiac arrest
- Out-of-hospital cardiac arrests account for more than a third of AMICS cases
- Pathophysiology differs from that of in-hospital cardiac arrest
- Mortality might differ from that of in-hospital cardiac arrest, and neurological complications are a frequent cause of death

Catheterisation laboratory
- Catheterisation laboratories are the optimal place for diagnosis of AMICS, because all diagnostic modalities are available (ie, invasive haemodynamics, echocardiography, point-of-care laboratory)
- Good scientific evidence exists to guide treatment of AMI (eg, revascularisation strategy, antithrombotic therapy)
- Mechanical circulatory support could be implanted on site

Intensive care unit
- Patients who develop cardiogenic shock while in the intensive care unit are not missed
- Advanced monitoring for assessment of changes in AMICS severity is available (ie, deterioration, response to treatment)
- Most patients are sedated and unconscious (unable to provide information, such as changes in symptoms and decision about treatment)

After cardiac surgery
- Few patients develop post-cardiotomy cardiogenic shock, but this proportion is high in heart failure centres
- Patients who have post-surgical cardiogenic shock are a very heterogeneous patient population and challenging to manage
- Many cases requiring MCS after surgery could be anticipated, but in some cases, MCS is emergently required

See Online for appendix

For further discussion and relevant publications, see appendix pp 1–3.
AMI=acute myocardial infarction. AMICS=AMI complicated by cardiogenic shock. MCS=mechanical circulatory support.

different study groups. For each pair of study participants, the patient who survived is designated the winner if the other patient died. If both participants in a pair survived, the winner is the first in a pair to be organ-support free. If the duration of organ support is similar (eg, within 1 day) or identical for two study participants in different study groups, they could be considered tied.[46] The win ratio is computed by dividing the total number of winners by the total numbers of patients, and the ratio (0 to 1) describes the estimated probability that an individual randomly selected from one study group will have a higher score (more favourable outcome) than an individual randomly selected from the other study group(s). Reporting a combined endpoint with the win ratio gives appropriate priority to the more clinically important events.

The global rank score uses a different approach. Each patient is assigned a rank from 1 to total sample size of the trial (ie, n) according to their response on several outcomes. Outcomes are arranged in a hierarchy, with the most adverse response (eg, early death) at the top (ie, rank=1) and the highest rank of n assigned to the patient with the most favourable response on any of the criteria. The analysis then involves a comparison of these ranked values between the treatment groups.[47] Notably, the hierarchy of outcomes could be personalised by taking into account patients' perspectives on preferred health states—eg, survival should be considered in the context of good health or quality of life rather than crude survival alone. Special attention should also be given to non-cardiac outcomes (eg, neurological adverse events).

Finally, the outcome of days alive and out of hospital is calculated by subtracting the number of days since death, or spent in hospital, from a follow-up time for each patient. This endpoint is patient-centred and meaningful to diverse stakeholders, and attractive for pragmatic trials given the ease of assessment. Such pragmatic endpoints other than mortality might be considered, in particular, for patients in SCAI shock stages A or B (ie, with low mortality) who are receiving drug therapies with an acceptable safety profile. Other surrogate endpoints such as arterial pressure, cardiac index, tissue perfusion, or the number of failing organs have been shown to be poorly correlated with improvement in survival and should be avoided.

An additional challenge when selecting study outcomes is establishing the ideal duration of follow-up for assessment of efficacy. The need for long-term follow-up in a disease with such high in-hospital or 30-day mortality is questionable. In-hospital survival should be the primary endpoint in most instances, but in studies of moderate size, modest benefits in mortality might be apparent only during longer-term follow-up. Indeed, in the SHOCK trial, the early invasive approach did not reduce 30-day mortality, but after 6 months there was a significant survival benefit.[6] Follow-up durations of longer than the hospital stay or 30 days have been problematic in older studies with very high mortality rates or in enriched populations of very sick or elderly patients (with few survivors), but if the expected survival rate is relatively high, longer follow-up is needed to assess the effects of interventions. In addition to survival, important measures for long-term follow-up include disability, major system complications affecting quality of life, patient-reported outcomes, and economic and social aspects of recovery. The road towards optimal trial

design is summarised in figure 3 and further detailed discussion of ways to improve trial design for critical care research is available elsewhere.[48]

Special considerations

Clinical studies require approval from ethics committees, which are mandated to verify that trials are ethical with regard to at least three major principles: autonomy (ie, patients' ability to decide to participate in a study after being adequately informed and without negative consequences in the case of refusal), beneficence (ie, intention to maximise benefits for the research project while minimising risks to research participants), and justice (ie, reasonable, non-exploitative, well considered study procedures that are fairly and equally administered). Performing clinical studies in critically ill patients, particularly in patients with cardiogenic shock, is challenging for several reasons. The beneficence of a study is difficult to assess because both the condition and the tested therapeutic measures are associated with a high risk of mortality and morbidity. Furthermore, cardiogenic shock per se might preclude direct informed consent by the participant (eg, because of inadequate cerebral perfusion, lack of time, or sedation), and relatives might be uncomfortable providing consent as surrogate decision makers. One possible strategy could be the process of so-called community consent. The community consent consists of a community consultation approved by the local ethics committees to gather information regarding community members' attitudes and beliefs related to the appropriateness and acceptability of the design, risks, and benefits of the planned research. Participants are enrolled into clinical trials without prospective informed consent and are informed afterwards with an opportunity to withdraw consent. We advocate waiver of the conventional consent process in severe AMICS in favour of community consent in agreement with patient associations and with approval of local ethics committees. The preparation of appropriate consent documents for multicentre and international trials might be especially challenging in the EU owing to different regulations, customs, and cultural differences between countries. Thus, the previous contact-seeking advice with local ethics committees and national regulatory bodies, on whether a trial can be performed in the specific country in the planned form, might be a reasonable precaution.

Other ethical issues might be raised by the investigators or sponsors of an RCT. The term unethical could reflect a lack of confidence in trying a new approach, but currently cardiogenic shock provides true equipoise. Indeed, despite the fact that testing a new treatment for AMICS might be considered risky (or unethical) because of the potential for adverse events with the new treatment, clinicians and trialists need to acknowledge that few advances in the management of AMICS have been achieved in the past 30 years, and continuing with the same failed strategies might also be regarded as unethical. The medical community recognises that no established treatment exists for several diseases and considers it ethical to do RCTs in those fields. For cardiogenic shock, despite many negative or neutral trial results over the past few decades, the notion persists that this condition is a pump failure alone, requiring restoration of pump function, resulting in reticence to test interventions that target alternative mechanisms, which might be viewed as too risky or unethical. However, an innovative approach, beyond the cardio-centric view of cardiogenic shock, might open the way for new treatments.

Patient associations and regulators should be involved in study design for several reasons. First, the study should be ethical and feasible from a patient perspective to minimise distress, consent withdrawals, and drop-outs. Second, endpoints should be meaningful for both clinicians and patients (survival with good health or quality of life is frequently mentioned by patient representatives as the desired outcome). Third, investigators should adhere to guidelines published by regulators, which often indicate the preferred study design and endpoints.

Special considerations applicable to different clinical scenarios (ie, prehospital setting, out-of-hospital cardiac arrest, catheterisation laboratory, intensive care unit, and after cardiac surgery) are summarised in panel 2 and appendix pp 1–2.

Search strategy and selection criteria

Before the Critical Care Clinical Trialists Workshop, authors searched MEDLINE for articles published in English, focusing on papers published during the 5 years up to Feb 1, 2020, relevant to their particular topic(s) using the search terms "acute myocardial infarction" and "cardiogenic shock", with other terms selected by the authors as they completed searches on their topic(s). A final MEDLINE search was done on Dec 1, 2020, as the paper was prepared for publication to update and refine the literature review. Authors also selected publications from their own files. The final list of cited articles was derived from the suggested articles provided by the authors and adapted to support the statement presented in this Position Paper. ClinicalTrials.gov was also searched for ongoing trials.

Conclusions

There is an increasing number of ongoing trials testing new therapies for cardiogenic shock, mostly funded by public institutions both in Europe and the USA. The design of new trials of interventions for AMICS needs to be more homogeneous than it has been in the past to enable combinations and comparisons of individual data in meta-analyses. Proposed improvements include the use of more homogeneous selection criteria that could be enriched by novel biomarkers. In addition, although

devices have shown promising results, research on novel therapies should be promoted. The combination of optimal use of novel therapies and devices should also be assessed, keeping in mind that some therapies might be more beneficial during early-stage cardiogenic shock, whereas others might be more effective in later disease stages.

Contributors

AM organised the workshop, invited participants, and chaired the sessions. All participants performed a literature search and gave a presentation on one or two topics; all participants participated in the discussion, and contributed to the paper by providing a summary of their presentation and by critically reviewing the manuscript. MA and AM actively participated in the workshop and drafted the manuscript, table, panels, and figures. SP, DAB, JP, NA, AB-G, LB, BF, EG, MG, NKK, MKa, MKo, PL, BL, YR, HT, UZ, and MOH actively participated in the workshop, did literature searches (before the meeting and as part of the manuscript preparation), and critically reviewed the manuscript.

Declaration of interests

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