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Glimpse into the future

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Randomized studies attempting to prove benefit of mechanical circulatory support in cardiogenic shock have failed to reduce the risk of death. Further, both registry and randomized data suggest increased rates of serious complications associated with these devices. This last review in the supplement discusses current evidence and provides a perspective on how the scientific community could advance cardiogenic shock research focused on mechanical circulatory support.

Introduction

Scientific progress in the field of cardiogenic shock (CS) faces the challenge of randomizing critically ill patients where immediate management is key to survival and obtaining informed consent of unconscious patients is notoriously difficult. The heterogeneity and multiple phenotypes of CS pose further complexity in conducting science in this field. Here, we report the experience of centres that have performed randomized clinical trials (RCTs) in patients with CS and refractory cardiac arrest (CA). It is likely that these centres will continue to use mechanical circulatory support including venoarterial extracorporeal membrane oxygenation (V-A ECMO) and percutaneous ventricular assist devices (pVADs) in highly selected patients although in a lower number as in previous settings before the ECLS-SHOCK[1] trial was published. Additionally, we discuss the best practices that will likely provide a pragmatic platform for daily management and for future trials that aim to address many of the uncertainties that remain such as adequate patient selection, optimal timing, concomitant vasoactive treatment, sedation, and ventilation strategies. Some, but not all, of these uncertainties will be resolved in future studies like RECOVER 4, UNLOAD ECMO, and ALT-SHOCK.

What do we know from randomized trials today?

There are only a few adequately powered RCTs that have examined the use of pVAD in CS caused by acute myocardial infarction (AMI-CS) (*Table 1*). Despite some positive effects on haemodynamics, none showed an improvement in outcomes. The IABP-SHOCK trial, which included 40 patients with AMI-CS, observed no significant reduction in disease severity in patients with intra-aortic balloon pump (IABP) compared with the use of vasopressors and inotropes alone.[4] The largest RCT of pVAD in AMI-CS to date is the IABP-SHOCK-II trial, which included 600 early re-vascularized patients with AMI-CS randomly assigned to routine IABP use vs. medical therapy alone.[5] Mortality at 30 days was similar with IABP and control [relative risk (RR), 0.96; 95% confidence interval (CI): 0.79–1.17]. This lack of efficacy and a potentially increased risk for complications with routine IABP use in AMI-CS[14] led to a Class III level of evidence B recommendation in recent guidelines.[15]

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Table 1 Publications of randomized clinical trials examining the effect of percutaneous ventricular assist device in cardiogenic shock caused by acute myocardial infarction

RCT	Year of publication	*N*	Mortality control (%)[a]	Mortality intervention (%)[a]	Complications/comments
IABP vs. medical therapy					
Arias *et al.*[2]	2005	40	55.6	32.3	Improved haemodynamics with IABP (PCWP; CI).
TACTICS[3]	2005	57	33.3	30.0	Complications were equally distributed. Study was stopped early due to slow enrolment (planned $n = 538$).
IABP-SHOCK[4]	2010	40	28.6	36.8	No improvement in haemodynamics with IABP.
IABP-SHOCK II[5]	2012	598	41.3	39.7	Complications were equally distributed.
TandemHeart vs. IABP					
Thiele *et al.*[6]	2005	41	45.0	42.9	Improved haemodynamics but more complications with the TandemHeart intervention.
Burkhoff *et al.*[7]	2006	33	35.7	47.4	Study was stopped early due to slow enrolment (planned $n = 90$).
mAFP vs. IABP					
ISAR-SHOCK[8]	2008	26	46.2	46.2	Improved haemodynamics with mAFP.
IMPRESS in severe shock[9]	2017	48	50.0	45.8	More bleeding was reported with mAFP intervention.
IMPELLA-STIC[10]	2020	12	0	33.3	More bleeding was reported with mAFP. Study was stopped early due to slow enrolment (planned $n = 60$).
V-A ECMO vs. medical therapy/rescue ECMO					
ECLS-SHOCK I[1]	2019	42	33.0	19.0	Complications were equally distributed.
ECMO-CS[11]	2022	117	47.5	50.0	Complications were equally distributed.
EURO-SHOCK[12]	2023	35	61.1	43.8	More vascular and bleeding complications were reported with V-A ECMO.
ECLS-SHOCK[13]	2023	420	49.0	47.8	More vascular and bleeding complications with V-A ECMO

AMI-CS, acute myocardial infarction complicated by cardiogenic shock; CI, cardiac index; ECLS, extra corporeal life support; IABP, intra-aortic balloon pump; mAFP, micro-axial flow pump; pVAD, percutaneous ventricular assist device; PCWP, pulmonary capillary wedge pressure; RCT, randomized controlled trial; V-A ECMO, venoarterial extracorporeal membrane oxygenation.

[a]In-hospital or 30-day mortality, respectively.

Some earlier RCTs showed greater haemodynamic improvements with pVAD compared with IABP in AMI-CS.[6-8,10,16] An individual meta-analysis of those small, and likely underpowered, RCTs that included 148 patients from four trials did not find a difference in survival between pVAD and IABP groups (pooled RR, 1.01; 95% CI: 0.70–1.44), and complications increased with pVAD use.[16] Unfortunately, some of these trials were stopped prematurely because of slow enrolment. In addition to being underpowered for the endpoint mortality, these studies were partly limited by patient selection criteria.[17] For example, the IMPRESS in severe shock trial ($n = 48$) enrolled patients with high-risk AMI-CS requiring mechanical ventilation with nearly all of whom had experienced CA. The in-hospital and 6-month mortality were similar with IABP and micro-axial flow pump (mAFP) and anoxic brain injury was the cause of death in roughly half of the deceased patients.[9]

The ECLS-SHOCK pilot study examined 30-day and 1-year mortality in 42 patients with AMI-CS who were randomly assigned to V-A ECMO vs. no pVAD. No differences in mortality, major complications, or neurologic outcomes at either time point were observed between the groups.[1,18] The multi-centre ECMO-CS trial compared a strategy of early V-A ECMO vs. rescue V-A ECMO in 122 patients with CS of SCAI SHOCK Stage D or E of various aetiologies (two-thirds due to AMI), which excluded comatose patients after CA.[11] Delayed (rescue) V-A ECMO was used in 39% of the control group. The ECMO-CS trial did not demonstrate a significant difference between the groups in the 30-day composite primary endpoint of death, resuscitated CA, or escalation of pVAD [63.8% vs. 71.2% respectively; hazard ratio (HR) 0.72; 95% CI: 0.46–1.12; $P = 0.21$]. Similarly, the 30-day all-cause mortality did not differ between groups (50.0% vs. 47.5%, respectively), and serious adverse events were also frequent in both groups (60.3% vs. 61.0%).[11] The EURO-SHOCK trial, which was stopped before completion of recruitment, included 35 patients randomized to standard therapy ($n = 18$) or V-A ECMO ($n = 17$). Thirty-day all-cause mortality occurred in 43.8% of patients who received V-A ECMO and in 61.1% of patients that received standard therapy (HR 0.56, 95% CI: 0.21–1.45; $P = 0.22$). All-cause mortality was 51.8% in the V-A ECMO group and

81.5% in the standard therapy arm (HR 0.52, 95% CI: 0.21–1.26; $P = 0.14$) at 1 year, with more vascular and bleeding complications reported in the V-A ECMO arm (21.4% vs. 0% and 35.7% vs. 5.6%, respectively).[12]

The recent ECLS-SHOCK trial provided insight that routine use of V-A ECMO in AMI-CS does not improve 30-day survival but exposes patients to the risk of bleeding complications and leg ischaemia.[13] The ECLS-SHOCK enrolled both ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) AMI-CS patients but excluded patients with refractory CA. Thus, the because of enhancement of shock risk criteria, the final population was composed of >77% of patients resuscitated from cardiac arrest before randomization leading to fatal brain injury in ~26% of patients dying until Day 30 without a significant difference between treatment groups. Despite including a high-risk population (median lactate level = 6.8 mmol/L), no subgroup appeared to benefit from V-A ECMO. This is also supported by the recent individual patient-based meta-analysis based on all four available RCTs applying V-A ECMO in AMI-CS.[19]

In summary, no RCT has shown any mortality benefit of mechanical circulatory support in patients with CS, and no subgroup has been identified either. This is further supported by a multitude of large propensity-matched analyses of micro-axial flow pump (mAFP) use vs. control, in which majority of cases indicate higher mortality and significantly higher complication rates with mAFP use.[20-26] However, even the most sophisticated statistical adjustments cannot account for unmeasured confounders in observational studies. Disease severity, anticipated prognosis, resuscitation status, goals of care, patient preferences, and institutional changes over time influence the decisions to use a pVAD, yet they are typically not captured in administrative or claims databases. The available evidence currently questions if any subgroup, which probably is <5% of all CS patients, has a mortality benefit. Therefore, the upcoming DanGer Shock trial (ClinicalTrials.gov NCT01633502) targets a more homogenous population with more restrictive enrolment criteria excluding comatose CA and NSTEMI patients.

If we consider the most recent data generated in the setting of extracorporeal cardiopulmonary resuscitation (eCPR)[27] and the wide application of pVAD for refractory CA, the optimal patient selection has not been proved, and we will continue to face patients who present with CS following resuscitation. This sparks the questions of how to proceed afterwards and when does resuscitation stop and CS begin. To date, eCPR trials have reported low rates of need for prolonged support and/or heart replacement therapies. Moreover, CA is not necessarily caused by primary ventricular failure, which calls for a critical appraisal of every single patient detail when analysing results. However, it is not only the high rate of resuscitated patients included in RCTs that may have contributed to those neutral results, but the inclusion of patients with multi-organ failure also poses challenges. If enrolled when organ failure is refractory, pVAD is unlikely of benefit.[28] On contrary, inclusion of patients without multi-organ failure may expose lower-risk CS patients to the risk of pVAD inherent complications that may outweigh any benefit.

What to expect and future needs

Technology

The greatest advantage created by the advancement of technology is the opportunity of time to safely wait for patient myocardial recovery and the ability to plan for eventual heart replacement therapies. Specifically, the haemocompatibility of current pVADs and the introduction in clinical practice of de-escalation and mobilization have dramatically changed the timeline of patient care and opened wide opportunities for heart team evaluation. Emergency listings for heart transplantation within days of extracorporeal life support (ECLS) and bridging from ECLS to durable left ventricular assist device (LVAD) are rarely performed because of the multi-morbidity and the age of the patients. As such, this calls for approaches that will assess outcomes and wiser allocation of highly valuable resources. New devices that will allow patient discharge without the need of surgery with full sternotomy and cardiopulmonary bypass are in the pipeline with safety and first-in-man studies currently under way. Still, there is a need for smaller and smarter devices with placement that allows safe mobilization, with minimal need for sedation, and reduced risk of bleeding and haemolysis.

Strategies

It is clear that multi-device strategies across the different stages of CS are commonly adopted in the current era and are being further tested in ongoing RCTs, including the UNLOAD ECMO trial (ClinicalTrials.gov NCT05577195). Indeed, once the patient is successfully resuscitated and stabilized from SCAI Stages E–C, it is reasonable to assume that the powerful platform deployed at presentation is no longer necessary. On the other hand, a change of approach might portend the risk of complications due to its invasiveness. From a methodological perspective, it is clear that a single trial on a single intervention would not address the gaps of knowledge and evidence. Thus, future studies should still incorporate contemporary escalation and weaning protocols. Similarly, the opportunities to qualify for LVAD or heart transplant are intrinsically related to patient characteristics, which are unable to be considered in any trial. These include general health status, haemodynamics of the right ventricle and pulmonary circulation, and ultimately the opportunity to undergo a high-risk procedure at times of economic and social constraints.

Ongoing randomized clinical trials

Ongoing RCTs examining temporary pVAD use in AMI-CS are summarized in *Table 2*, several of which are adequately powered for mortality assessment including the eagerly awaited DanGer Shock trial[29] and RECOVER IV (ClinicalTrials.gov NCT 05506449). Large international RCTs with adequate statistical power that include enrolment of a population that mirrors the typical AMI-CS population and exclude patients unlikely to benefit are essential to establishing standards of care. In addition to RCTs, observational studies will continue to provide additional value and important information in AMI-CS. However, there is a need to move away from retrospective analyses of administrative databases and focus on the prospective enrolment of CS patients in registries, irrespective of

Table 2 Ongoing randomized clinical trials on micro-axial flow pump in cardiogenic shock caused by acute myocardial infarction and other shock forms

Acronym	NCT	Planned *N*	Already recruiting	Intervention	Primary endpoint
Populations with AMI-CS					
ANCHOR	NCT04184635	400	Yes	V-A ECMO	At Day 30, treatment failure was defined as death in the V-A ECMO group and death or rescue V-A ECMO in the control group.
DanGer Shock	NCT01633502	360	Yes	Impella CP	All-cause mortality through 180 days.
ULYSS	NCT05366452	204	Yes	Impella CP	All-cause mortality through 30 days.
RECOVER IV	NCT05506449	560	No	Impella CP	All-cause mortality through 30 days.
Patients with CS receiving ECMO					
UNLOAD ECMO	NCT05577195	198	Yes	Impella CP	All-cause mortality through 30 days.
REVERSE	NCT03431467	96	No	Impella CP	Recovery from cardiogenic shock.
ECMOsorb	NCT05027529	54	Yes	Cytosorb	Change in Vasoactive Inotropic Score after 72 h.
CLEAN ECMO	NCT05642273	60	Yes	oXiris membrane	Change in Vasoactive Inotropic Score on Day 0 and Day 2.
AMI + pre-shock/at risk					
STEMI-DTU	NCT03947619	668	Yes	Impella CP	Infarct size normalized to the LV mass (evaluated via cardiac MRI)
UNLOAD AMI	NCT04562272	80	Yes	Impella CP	Difference in the LV end-systolic volume at Days 5–7 and 3 months.
SCAI-B	NCT04989777	512	No	IABP	MACE within 30 days.
None AMI-related CS and cardiac decompensation					
Altshock-2	NCT04369573	200	Yes	IABP	Successful bridge to heart transplant or LV assist device implantation. Survival through 60 days.
UNLOAD-HF	NCT05064202	456	No	Impella CP	Composite of all-cause mortality, mechanical ventilation, renal replacement therapy and re-hospitalization or urgent visit for heart failure through 60 days.

AMI-CS, cardiogenic shock caused by acute myocardial infarction; IABP, intra-aortic balloon pump; LV, left ventricular; MRI, magnetic resonance imaging; mAFP, micro-axial flow pump; MACE, major adverse cardiovascular events; V-A ECMO, venoarterial extracorporeal membrane oxygenation.

whether pVAD is used or not. Dedicated case report forms should be used to document the reasons for pVAD device usage, shock stage, and other critical prognostic factors and to adjudicate outcomes.

The ability to identify the patients likely to benefit, experience a neutral effect, or be harmed by pVAD is essential to design future RCTs. Some may argue that CS is an area where RCTs are inadequate given the complexity and heterogeneity of the condition. However, to use these costly devices that are accompanied by serious complications, with little to no evidence of a benefit except expert consensus and uncontrolled biased registry, studies cannot be the answer. Thus, the scientific community should come together and continue to perform adequately powered RCTs in more targeted populations and the use of these devices should optimally be restricted to controlled settings.

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Data availability

No new data were generated or analysed in support of this research.

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