Trials of mechanical circulatory support with percutaneous axial flow pumps in cardiogenic shock complicating acute myocardial infarction: Mission impossible?

Étude clinique sur l'assistance circulatoire par pompe microaxiale dans le choc cardiogénique compliquant un infarctus du myocarde : mission impossible ?

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Abbreviations: AMI, acute Myocardial Infarction; AMICS, Acute Myocardial Infarction Complicated by Cardiogenic Shock; CS, Cardiogenic Shock; ECMO, Extracorporeal Membrane Oxygenation; IABP, Intra-Aortic Balloon Pump; pAFP, Percutaneous Axial Flow Pump; PCI, Percutaneous Coronary Intervention; RCT, Randomized Controlled Trial.

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Summary Cardiogenic shock is a complex clinical entity associated with very high mortality and intensive resource utilization. Despite the widespread use of timely reperfusion and appropriate pharmacotherapy, the survival rate remains at around 50%. Recently, percutaneous axial flow pumps have been integrated into the therapeutic spectrum of cardiogenic shock management. However, most of the literature supporting their use stems from observational studies. To date, attempts to perform randomized controlled trials with percutaneous axial flow pumps have failed. This underlines the challenge of performing a well-conducted randomized controlled trial that provides the highest level of evidence. Such a trial is warranted, because percutaneous axial flow pumps are costly, and are associated with serious complications. The major pitfalls of previous studies were lack of standardized cardiogenic shock definitions according to clinical severity, inappropriate patient and device selection, lack of standardized trial endpoints and high rates of crossovers; these issues must be carefully considered and evaluated. In light of recent trial failures, we aim to summarize the challenges associated with performing randomized controlled trials of percutaneous axial flow pumps in patients experiencing acute myocardial infarction complicated by cardiogenic shock, and to suggest potential means of overcoming them.

MOTS CLÉS
Choc cardiogénique ;
Étude ;
Infarctus du myocarde ;
Étude clinique randomisée ;
Support circulatoire mécanique

Résumé Le choc cardiogénique reste une entité clinique complexe associée avec une très haute mortalité et une utilisation intensive de ressource. Malgré la généralisation de la reperfusion précoce et un traitement adapté, le taux de mortalité reste élevée aux alentours de 50 %. Les pompes axiales percutanées ont été récemment intégrées dans l'arsenal thérapeutique du choc cardiogénique. Cependant, la plupart des données de la littérature en faveur de leur utilisation sont de natures observationnelles. À ce jour, les tentatives de réaliser les études cliniques randomisées ont été des échecs. Cela souligne à quel point il reste compliqué de réaliser une étude randomisée bien conduite afin de fournir un niveau de preuve suffisant. Une telle étude est nécessaire car les pompes axiales sont coûteuses et associées avec des complications sérieuses. L'absence de définition standardisée du choc cardiogénique en fonction de sa gravité, une mauvaise sélection des patients ou des interventions, l'absence de critère de jugement validé et le fort taux de *crossover* sont parmi les écueils majeurs de la réalisation des précédentes études et doivent être prise en compte pour la réalisation des prochaines. À la lumière des échecs récents, nous avons voulu résumer les écueils pour la réalisation d'une étude randomisée utilisant les pompes microaxiales dans le choc cardiogénique secondaire à un IDM et suggérer des voies potentielles de résolution.

Background

Cardiogenic shock (CS) is the leading cause of death in patients experiencing acute myocardial infarction (AMI) [1]. Despite the widespread use of early revascularization, the prevalence is stable, and the associated mortality rate remains high (30—50%), with little improvement in recent years [1,2]. Therefore, there is an unmet need for alternative strategies that could improve outcomes [3]. Percutaneous axial flow pumps (pAFPs) have emerged as an attractive treatment option in CS, because of their ability to restore vital organ perfusion and prevent irreversible organ damage. Thus, they have the potential to favour recovery and lower mortality [4]. Whereas intra-aortic balloon pumps (IABPs) failed to show a clinical benefit in patients with acute myocardial infarction complicated by cardiogenic shock (AMICS), new pAFPs, which provide superior haemodynamic support, may represent a new opportunity to tackle CS and improve outcomes [5,6]. These devices efficiently decrease myocardial workload by unloading the left

Table 1 Challenges for randomized clinical trials in cardiogenic shock following acute myocardial infarction, and potential means of overcoming these challenges in future studies.

Limitation	Challenge	Potential means of overcoming the challenge
Definition of CS	Various severity states	ACC new definition
Severity of CS	Wide CS spectrum, from preshock to refractory CS	Select patients with stage B to D; exclude patients in refractory CS with multiorgan dysfunction (stage E)
Timing of revascularization	Heterogeneity in timing of revascularization	Exclude MI > 12 h and fibrinolysis
Timing of MCS implantation	When to intervene	At the time of coronary angiography, before PCI
Cardiac arrest	Neurological outcome unknown	Exclude patients with long or refractory CA (NF and LF > 5 min); prespecified subgroup analysis of patients with previous CA
MCS	MCS with best risk/benefit ratio and widely available	AFP (Impella CP®) for stage C to D; VA-ECMO for stage E or failure of AFP
Informed consent	Obtaining informed consent in this critical setting with patients intubated and mechanically ventilated or with altered mental status	Dedicated informed consent process for patients unable to consent: consent from relatives or family members; patient's will assessed by two independent physicians in the absence of family members
Outcome variable	Which outcome measure to use and when to assess it	Mortality and need for VA-ECMO, LVAD or heart transplant at 1 month
Control group	Lack of gold standard	A standardized protocol based on the literature, including which drugs to use and with what objective: SBP $\geq$ 90 mmHg; MBP $\geq$ 65 mmHg; lactate clearance, $ScVO_2$ > 65%
Large sample size	Difficulties in including a large number of patients	Multicentre international effort and secured resources; pragmatic trials; randomization by centre cluster

ACC: American College of Cardiology; AFP: axial flow pump; CA: cardiac arrest; CS: cardiogenic shock; LF: low flow; LVAD: left ventricular assist device; MBP: mean blood pressure; MCS: mechanical circulatory support; MI: myocardial infarction; NF: no flow; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; $ScVO_2$: central venous oxygen saturation; VA-ECMO: venoarterial extracorporeal membrane oxygenation.

ventricle, and therefore may also favour recovery and prevent remodelling [7,8]. Moreover, these devices can be implanted quickly, and could be widely available in catheterization laboratories, thus reducing time to support. However, evidence for the use of pAFPs in AMICS from randomized controlled trials (RCTs) is lacking [6]. Scarcity of available data is a major obstacle to the implementation of new therapeutic strategies, which would include pAFPs in this clinical setting. In addition, the high costs and complication rates associated with pAFPs warrant appropriate evaluation. Questions abound regarding the challenges that limit the conduct of RCTs and the alternative sources of clinical evidence that could be provided in AMICS. In the present manuscript, we aim to summarize the main challenges facing successful RCTs of pAFPs in AMICS, and the means to overcome them (Table 1).

Recent RCTs of mechanical circulatory support in AMICS

In an evidence-based approach to evaluate medical interventions, RCTs are the gold standard. Whereas the advantages of RCTs include quantitative and comparative inferences of treatment efficacy with less bias, disadvantages include highly selective inclusion criteria and standardized interventions [9]. However, conducting an RCT in AMICS may be highly problematic, because of difficulties in selecting, enrolling and randomizing these patients, as discussed below [10]. However, considering the high incidence of AMI and the high mortality of CS, any intervention that reduces mortality is likely to have major public health implications, and should be evaluated adequately. The large number of attempts to perform such trials illustrates the great-unmet clinical need (Table 2). To date, four RCTs have aimed to compare the clinical outcome of patients with AMICS with pAFPs or IABPs, but none was completed. Only one trial investigating the haemodynamic properties of pAFPs was performed successfully. The ISAR-SHOCK study compared the haemodynamic effects of a pAFP and an IABP, suggesting superiority of the pAFP [10]. The IMPELLA-STIC randomized trial was discontinued after enrolment of only 15 patients out of 60 over 34 months [11]. The RECOVER II trial, comparing the Impella 2.5® (Abiomed Inc., Danvers, MA, USA) with an IABP in CS, was initially designed to include 384 patients, but was also discontinued after 18 months because of slow inclusions and funding issues. Furthermore, in the IMPRESS in Severe Shock trial, only 48 patients out

Table 2 Randomized clinical trials of Impella in chronological order.

Study	Clinical trial identifier	Condition	Number of sites	Patients required (*n*)	Patients enrolled (*n*)	Duration (months)	Status	Reason for discontinuation; comment
FRENCH TRIAL (2006)	NCT00314847	AMICS	13	200	19	52	Discontinued	Low enrolment; not published
ISAR-SHOCK (2006)	NCT00417378	AMICS	2	26	26	19	Completed	Haemodynamic assessment; not randomized
IMPRESS in STEMI (2007)	NTR1079	STEMI; preCS	1	130	18	22	Discontinued	Low enrolment
RECOVER I FDA (2008)	NCT00596726	PCCS	7	Up to 20	17	28	Completed	Feasibility study
RECOVER II FDA (2009)	NCT00972270	AMICS	11	384	1	18	Discontinued	Low enrolment: 11 active sites, 50 IRB approved
RELIEF I (2010)	NCT01185691	ADHF	1	20	1	33	Discontinued	Low enrolment
DANGERMANSHOCK (2012)	NCT01633502	AMICS	3	360	~100	78	Enrolling	Ongoing
IMPRESS Shock (2004)	NTR3450	STEMI-CS; mechanical ventilation	1	> 100	48	52	Discontinued[a]	Low enrolment

ADHF: acute decompensated heart failure; AMICS: acute myocardial infarction complicated by cardiogenic shock; CS: cardiogenic shock; IRB: Institutional Review Board; PCCS: postcardiotomy cardiogenic shock; STEMI: ST-segment elevation myocardial infarction.

[a] Interim analysis found that the trial was underpowered because of higher than expected survival, therefore > 100 patients were needed to show a mortality difference between the two groups; the trial was continued with 48 patients as an exploratory safety study only.

of the 130 previously planned were enrolled [12]. The DANSHOCK trial is the fifth, and only currently ongoing, active attempt to randomize patients in the AMICS setting to a pAFP versus medical therapy, and has enrolled around 100 patients to date; this is far from the 360 planned patients, despite more than 5 years of inclusions. The trial is currently adding new centres in an attempt to prevent discontinuation. The recurrent theme observed with RCTs evaluating pAFPs in AMICS has been the low and slow enrolment rates related to ethical, logistical and methodological challenges. In addition, several other challenges need to be overcome to prevent further failures, including costs.

Challenges for RCTs in CS

The main challenges to overcome are summarized in Table 1.

Patient selection

CS is a state of critical end-organ hypoperfusion caused by reduced cardiac output, which is ill defined and challenging to diagnose. The European Society of Cardiology proposes these diagnostic criteria: systolic blood pressure < 90 mmHg for > 30 min (or the need for vasopressors to achieve SBP $\geq$ 90 mmHg), together with pulmonary congestion or elevated left ventricular filling pressures and signs of impaired organ perfusion [13]. CS includes a large spectrum of clinical settings that range from mild hypoperfusion to profound refractory shock with multiorgan dysfunction. In addition to the various severity states, some patients (such as those with hypoperfusion, but without hypotension) have a similar prognosis to those with CS [14]. Moreover, further patients may have various delays to evolution: some present crash-and-burn CS, whereas others show a slowly developing low output state following acute heart failure, without initial shock. Overall, the lack of clear-cut criteria for CS and the variable severity make it difficult to enrol a homogenous population in an RCT [15].

It is challenging to differentiate patients with CS who have not passed the window of opportunity for treatment from those who have irreversible organ damage despite normalization of haemodynamic variables [16]. In fact, despite similar pathophysiology, there is wide heterogeneity in AMICS: patients may present an ST-segment elevation or a non-ST-segment elevation myocardial infarction; they may have had revascularization on time, outwith the 12-hour deadline or not at all; and they may have mechanical complications [15]. Obviously, the adequate choice of RCT inclusion and exclusion criteria is the key to accurately demonstrate the efficacy of an intervention. Therefore, in order to select a homogenous and treatable study population, future trials require highly selective inclusion criteria based on clinical settings, age, co-morbidities, patient history, timing of the AMI and the intervention and haemodynamic and biological characteristics. This will insure a fair evaluation of the intervention, and will prevent futility or even harm.

Recently, Baran et al. proposed a new classification of CS from stage A to stage E, depending on clinical findings and evolution. This classification has subsequently been shown to predict clinical outcome, and may be useful to guide inclusion criteria [17]. The inclusion should target patients in stage C or stage D (classic CS), excluding patients at lower risk of mortality (stage A and stage B) or those who may require a higher level of support (stage E) [17,18].

To prevent futility, further inclusions should be limited to patients who have received revascularization with percutaneous coronary intervention (PCI) within 12 h of AMI onset and have recovery potential or are eligible for a long-term project. In Fig. 1, we propose a theoretical flowchart for inclusions. Because the stringent inclusion criteria limit the number of eligible patients, an international effort is required, with high-volume centres.

The specific case of CS following cardiac arrest

CS following cardiac arrest is a specific issue. Because of the difficulty in assessing neurological outcome, most of these patients cannot be included in an RCT. In the IMPRESS in Severe Shock trial, the investigators aimed to compare the Impella CP® (Abiomed Inc., Danvers, MA, USA) with an IABP in patients with ST-segment elevation myocardial infarction with severe CS and treated with primary PCI. In this trial, 48 patients were enrolled in 40 months, with 85% of them presenting AMI complicated by cardiac arrest. The investigators found that implantation of the Impella device did not induce a reduction in mortality. Nevertheless, this result could have been related to a lack of study power (130 patients were initially planned for this trial) and the fact that most deaths were related to anoxic encephalopathy, resulting in a futile trial [12]. This underlines an additional challenge in patients with CS with cardiac arrest for whom neurological outcome comes first. However, to allow a sufficient number of patients to be enrolled, patients with cardiac arrest should not be excluded altogether. In fact, in the recent Culprit-Shock study, 51% of patients had resuscitation before randomization [19]. Overall, only patients considered to have an optimal neurological prognosis (with either a very short duration of slow flow [< 5 min] or a lack of no flow) should be considered for an RCT [20] (Fig. 1).

How to choose the most promising assistance device?

Because of the lack of randomized trials, no device can yet be presented as the best or the ideal approach for all patients. Among the available devices, pAFPs appear appealing because of their wide availability and quick insertion time. In addition, they provide superior haemodynamic benefit compared with IABPs. For instance, in the ISAR-SHOCK trial, the improvement in cardiac index was significantly greater in the Impella group than in the IABP group (+29% vs +6%; $P = 0.02$) [10]. The haemodynamic support offered by a pAFP was also studied in a retrospective analysis of patients undergoing high-risk PCI, showing decreased renal impairment with the device [21]. However, a meta-analysis observed a modest haemodynamic effect with a pAFP, with improved mean arterial pressure and reduced lactate concentration, but only a trend toward increased cardiac index and decreased pulmonary capillary wedge pressure ($P = 0.1$ for both) [22]. Nevertheless, it is difficult to accurately assess their haemodynamic properties, as the output provided by the device substitutes for that of the

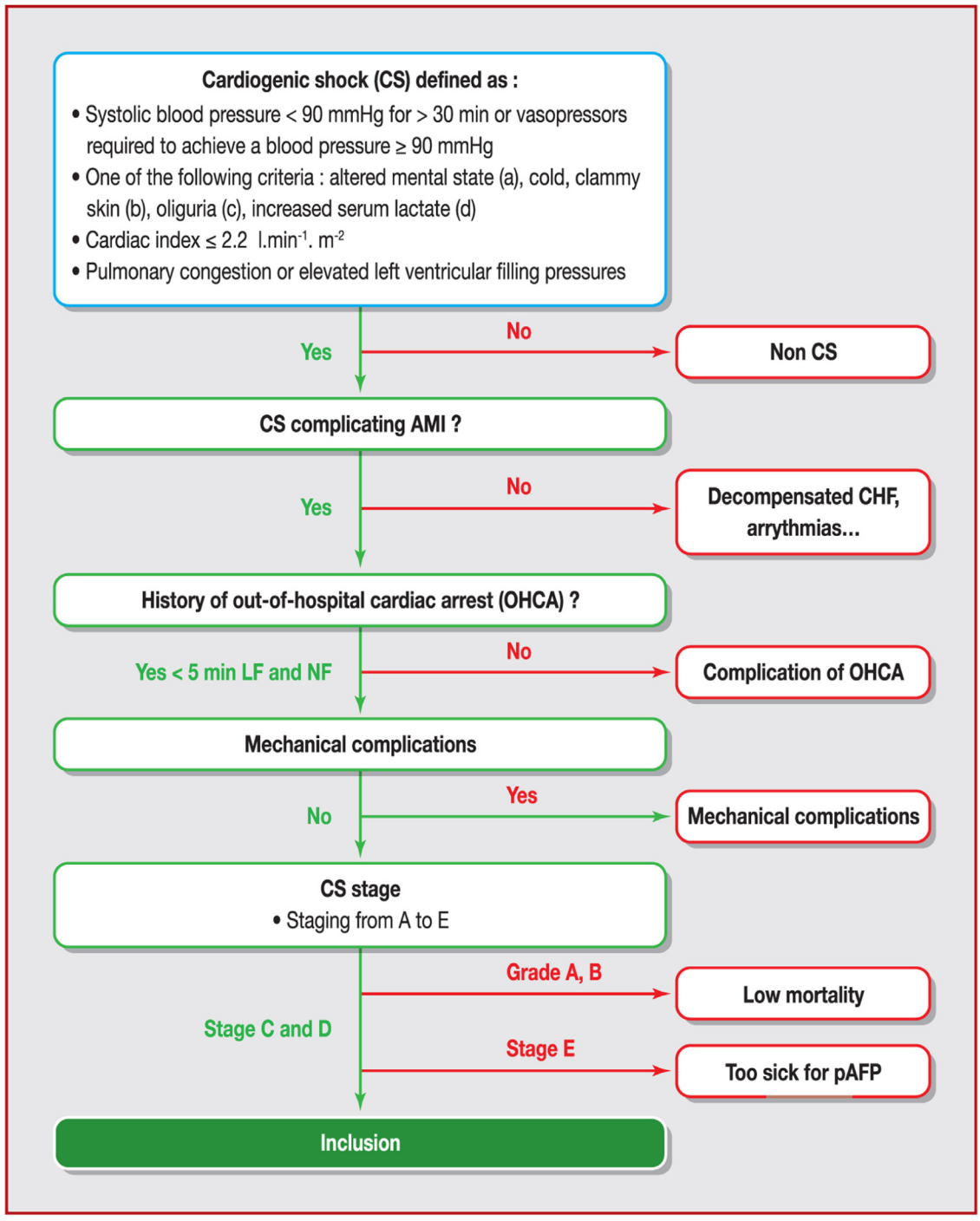

Figure 1. Theoretical flowchart for recruitment in randomized clinical trials of mechanical circulatory support. AMI: acute myocardial infarction; CHF: congestive heart failure; CS: cardiogenic shock; LF: low flow; NF: no flow; OHCA: out-of-hospital cardiac arrest; pAFP: percutaneous axial flow pump; RCT: randomized clinical trial.

native heart [23]. Although a pAFP is considered inferior to extracorporeal membrane oxygenation (ECMO) regarding blood flow, it possesses several advantages, such as its wide availability and quick insertion, which reduces time to support, provides anterograde flow and favours recovery through left ventricle unloading [11]. Therefore, pAFPs should be the focus of the next RCT in AMICS.

Assessing the risk-benefit ratio of mechanical circulatory support

All forms of mechanical circulatory support are associated with a wide range of potential side effects — particularly vascular and bleeding complications; these are summarized according to their incidence in Table 3. Some of these

Table 3 Adverse effects of short-term mechanical circulatory support [41].

	IABP (7.5—9 Fr)	Impella 2.5 and Impella CP	Impella 5.0	ECLS
Size of MCS	7.5—8 Fr	Motor 12/14 Fr; catheter 9 Fr	Motor 21 Fr; catheter 9 Fr	Arterial catheter 15—19 Fr; venous catheter 23—29 Fr
Very frequent (> 10%)	Thrombocytopaenia	Severe access vascular bleeding[a]	Severe access vascular bleeding[a]	Severe *access vascular bleeding*[a]; site infection
Frequent (5—10%)		Intravascular haemolysis; site infection	Limb ischaemia[b]; site infection	Limb ischaemia[b]
Non-exceptional (1—5%)	Device malfunction; severe limb ischaemia[b]; severe access vascular bleeding[a]	Limb ischaemia[b]; device malfunction; pump displacement	Intravascular haemolysis; device malfunction; pump displacement	Intravascular haemolysis; pulmonary haemorrhage
Exceptional (< 1%)	Retroperitoneal bleeding; intravascular haemolysis; aortic complication; cerebral embolism; paraplegia; site infection; mesenteric ischaemia; balloon leak	Retroperitoneal bleeding; functional mitral stenosis; mitral regurgitation (chordal rupture); LV wall perforation; intraventricular thrombosis	Functional mitral stenosis; mitral regurgitation (chordal rupture); aortic regurgitation; LV wall perforation; intraventricular thrombosis	Aortic complication; device malfunction

ECLS: extracorporeal life support; IABP: intra-aortic balloon pump; LV: left ventricular.

complications are not uncommon, and may reduce the ability of the pAFP to improve prognosis; they also represent an additional challenge, as the selection of patients for implantation is critical in order to prevent unnecessary harm. This is of particular interest, as there is a learning curve with pAFP use [24]. Further, recent registry data raised concerns regarding costs and potential harm related to adverse events associated with the use of pAFPs, further strengthening the need to perform an RCT of pAFPs in AMICS [25]. Because of the high risk of complications and the learning curve associated with device use, only centres with sufficient expertise should be allowed to participate in the dedicated RCT.

Difficulty in obtaining informed consent

Given the time-sensitive and life-threatening nature of AMICS, seeking informed consent from patients or their families can be difficult, and sometimes may not be possible. Moreover, because of the need for immediate treatment of AMICS, clinicians are faced with the ethical dilemma of obtaining informed consent for inclusion into a clinical trial versus providing the best treatment as soon as possible to improve outcome. A ''delayed consent'' model was used successfully in the setting of AMI in the HEAT-PPCI trial conducted in the UK. In this trial, patients with AMI were treated with either heparin or bivalirudin, based on randomization, and the consent to use their data was obtained afterwards [26]. In the CULPRIT-SHOCK study, a patient who was unable to consent could be randomized by two independent physicians who assessed their will (if possible by contacting their relatives), which facilitated inclusions in countries allowing this type of consent [19].

Choice of outcome variables

Conducting an RCT in CS requires a careful choice of primary endpoint. Not surprisingly, significant improvements in haemodynamic variables with pAFPs have been reported [27,28]. However, an improvement in haemodynamics with drugs and active circulatory assist devices has not always been associated with an effect on outcome [10,27]. Based on the haemodynamic improvements with pAFPs, a clinical benefit is expected in CS. Accordingly, the primary outcome of RCTs with pAFPs has been long- or short-term mortality. However, power calculations to detect significant differences in mortality outcomes require a large patient sample size. Furthermore, survival may not accurately encompass the overall benefit of a pAFP. In addition to mortality, the need for a long-term left ventricular assist device or heart transplant could be reduced, as the pAFP unloads the left

Table 4 Completed clinical trials of Impella in cardiogenic shock.

Study	Type	Patients receiving Impella (*n*)	Timing of Impella placement	Primary endpoint	Conclusions
Flaherty et al. [39]	Meta-analysis	379	Before versus after PCI	Mortality	Impella before PCI in patients with AMICS decreased in-hospital/30-day mortality by 48% compared with Impella after PCI
IMPRESS in Severe Shock [12]	Randomized trial	24	After PCI in 88%	Mortality	30-day mortality of 46% in patients on mechanical ventilation with AMICS and placement of Impella after PCI
ISAR-SHOCK [10]	Randomized trial	13	After PCI	Haemodynamic effect	Increase in CI after 30 min of Impella support
EUROSHOCK registry [42]	Observational	120	During PCI	Mortality	30-day mortality of 64.2%; significant decrease in lactate concentrations at 48 h
Detroit CSI [38]	Observational	41	Before PCI in 66%	Mortality	Survival to device explant in 85%; survival to discharge in 76%; 67% increase in cardiac power output after Impella versus before Impella; 71% of patients had reduction in inotrope and vasopressor support after Impella
IQ database [35]	Observational	15,259	Before PCI in 59% of 5571 patients	Mortality	Higher survival with: Impella use before PCI versus use as salvage therapy (59% vs 52%; $P < 0.001$); haemodynamic monitoring using PA catheters (63% vs 49%; $P < 0.0001$)

AMICS: acute myocardial infarction complicated by cardiogenic shock; CI: cardiac index; PA: pulmonary artery; PCI: percutaneous coronary intervention.

ventricle, promoting recovery. Based on previous trials in CS, in order to evaluate the clinical benefit of a pAFP, an accurate clinical endpoint should include mortality, escalation to extracorporeal life support and need for heart transplant or long-term left ventricular assist device at 1 month.

Lack of clinical equipoise (balance) and issues with crossover

Because of the scarcity of available data, current therapies in CS are based on a low level of evidence — mainly expert consensus. In fact, the current standard therapy in this clinical setting is based on a low scientific background. Therefore, most centres have homemade care protocols, and defining the gold standard therapy for the control group is a challenge. IABP is the comparator that has been used most widely in randomized trials of mechanical circulatory support in CS. However, the failure of the IABP SHOCK 2 trial suggests that it should no longer serve as a reference in the control group of an RCT [6,29,30]. Because of its high rate of complications, ECMO should also not be used as a reference in the control group.

Therefore, the comparator arm should be a clinical protocol agreed by all centres, including the use of inotropes and vasoconstrictors, with guidance for escalation steps, such as the need for ECMO in cases of failure. In addition, only high-volume centres with a dedicated shock team should be involved in such RCTs, as they provide optimal care and outcome [31—33].

An additional challenge with the management of patients randomized to the ''usual care'' arm is the crossover of patients that keep deteriorating clinically and haemodynamically in this group. In the EOLIA trial, for instance, the efficacy of ECMO was evaluated in patients with severe acute respiratory distress syndrome [34]. Patients were randomly assigned to immediate ECMO or conventional treatment, and mortality at 60 days was similar in the two groups. However, the crossover to ECMO in the control group occurred in 28% of patients. In order to limit this issue, we propose to use ECMO and not a pAFP when therapeutic escalation is required in both arms.

Table 5 Ongoing trials[a].

Clinical trial identifier	Study	Intervention	Primary endpoints	Number of centres	Patients included (*n*)	CS aetiologies
Observational trials						
NCT03528291	Transient Circulatory Support in Cardiogenic Shock (ALLOASSIST)	Observational	In-hospital mortality	?	240	Ischaemic and non-ischaemic
NCT02790242	Registry for Cardiogenic Shock: Utility and Efficacy of Device Therapy (RESCUE)	Observational	1-year survival after MCS device implantation	7	200,000	Ischaemic and non-ischaemic
NCT02697006	Synchronized Cardiac Assist for Cardiogenic Shock: The SynCor trial	Observational	Safety and efficacy of i-cor®[b] device implantation	1	48	Ischaemic = ACS
NCT02985008	SMart Angioplasty Research Team: A Multi-center, Open, REtrospective and Prospective Observational Study to Investigate Clinical oUtcomes and Efficacy of Left Ventricular Assist Device for Korean Patients With Cardiogenic Shock (RESCUE)	Observational	In-hospital mortality	?	1000	Ischaemic and non-ischaemic
NCT03378739	Implementation of a Cardiogenic Shock Team and Clinical Outcomes (INOVA-SHOCK Registry)	Observational	1-year mortality	1	400	Ischaemic and non-ischaemic
RCTs						
NCT03635840	The Effects of IABP Prior to Revascularization on Mortality of ACS Patients Complicated With Cardiogenic Shock	Randomized trial; parallel assignment	30-day mortality	1	92	Ischaemic = ACS
NCT03431467	Impella CP With VA ECMO for Cardiogenic Shock (REVERSE)	Randomized trial; parallel assignment	Survival free from HTx, LVAD or inotropes at 30 days	1	96	Ischaemic and non-ischaemic

Table 5 (*Continued*)

Clinical trial identifier	Study	Intervention	Primary endpoints	Number of centres	Patients included (*n*)	CS aetiologies
NCT02301819	ExtraCorporeal Membrane Oxygenation in the Therapy of Cardiogenic Shock (ECMO-CS)	Randomized trial; parallel assignment	Death from any cause, resuscitated circulatory arrest and implantation of another MCS device at 30 days	3	120	Ischaemic and non-ischaemic
NCT02544594	Clinical Study of Extra-Corporeal Life Support in Cardiogenic Shock Complicating Acute Myocardial Infarction (ECLS-SHOCK)	Randomized trial; parallel assignment	LVEF at 30 days	1	42	Ischaemic = ACS
NCT02870946	The Effect of Simultaneous Renal Replacement Therapy on Extracorporeal Membrane Oxygenation Support for Cardiogenic Shock Patients	Randomized trial; parallel assignment	30-daysmortality	1	262	Ischaemic and non-ischaemic
NCT01633502	Effects of Advanced Mechanical Circulatory Support in Patients With ST Segment Elevation Myocardial Infarction Complicated by Cardiogenic Shock: The Danish Cardiogenic Shock Trial	Randomized trial; parallel assignment	6-month mortality	7	360	Ischaemic = ACS/only STEMI
NCT03637205	Extracorporeal Life Support in Cardiogenic Shock (ECLS-SHOCK)	Randomized trial; parallel assignment	30-day mortality	?	420	Ischaemic = ACS

ACS: acute coronary syndrome; CS: cardiogenic shock; ECMO: extracorporeal membrane oxygenation; HTx: heart transplant; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; MCS: mechanical circulatory support; RCT: randomized clinical trial; STEMI: ST-segment elevation myocardial infarction; VA: venoarterial.

[a] Sixty-six studies were found to be registered on clinicaltrials.gov in September 2018 using the keyword ''cardiogenic shock''. Studies were deleted if they had been terminated or completed ($n = 26$), if they did not concern patients with CS exclusively ($n = 7$), if they had been withdrawn or if their status was unknown ($n = 4$) and if they had a retrospective design ($n = 4$). Only trials including patients with CS exclusively are presented: for instance, patients benefiting from percutaneous coronary intervention at high risk are not presented. Only studies concerning MCS support are presented ($n = 12$).

[b] Xenios AG, Heilbronn, Germany.

Alternative sources of clinical evidence for mechanical circulatory support, and the need for new therapeutic strategies

Taking all these challenges together, it appears that it is complex to identify and evaluate the ''right patient at the right time with the right device'' in the setting of an RCT. Given the difficulties in conducting large RCTs in CS, investigators will be left with alternative sources of evidence to answer questions related to the risks and benefits of mechanical circulatory support, until the barriers to RCT design and resources are overcome (Table A1).

Real-world evidence can bridge the gap, because of the large sample size and the ability to include critically ill patients who are typically under-represented in RCTs. These data provide valuable clinical evidence on the effectiveness of therapies in routine clinical settings [31]. For example, regarding pAFPs, clinical outcomes in AMICS have been analysed in the real world global Catheter-based Ventricular Assist Device (cVAD) registry and the Impella Quality (IQ) database [35]. The results from the cVAD registry suggest that the benefit of pAFP in CS is time dependent. In fact, early initiation of haemodynamic support with a pAFP within 90 min of shock onset, before escalating doses of inotropes and PCI, was associated with improved survival [36]. Similarly, results from the IQ database suggest improved survival in AMICS with pAFP use before PCI and haemodynamic monitoring by pulmonary arterial catheters [37]. In accordance with the available clinical evidence, four centres in Detroit collaborated to determine if following a uniform protocol, incorporating haemodynamic monitoring and early initiation of pAFP, would improve clinical outcomes in AMICS. Interestingly, the survival rate in this cohort was 76%, representing a significant improvement from institutional historical control rates of 50% [38]. These encouraging trends in survival in CS underscore the value of incremental care changes based on actionable research findings from real-world studies (Table 4) [38,39].

Until new evidence is available, these findings may encourage the implementation of new therapeutic strategies in a CS bundle, including the use of pAFPs in selected patients with CS. These observational data are critical in showing that not only a device, but a new therapeutic strategy, including early pAFP implantation, should be tested in future RCTs. In particular, it suggests that pAFPs must be inserted early in the therapeutic strategy, before PCI [34,40].

Although there is great interest in RCTs in CS, as evidenced by the numbers of trials currently enrolling patients, none of them has the ability to adequately address the challenges described above (Table 5).

Conclusions

CS represents a continuum of conditions, with variable aetiologies, severities and rates of progression. Hence, once identified, prompt therapeutic care and a strategy adapted to the severity of the shock are the keys to improving prognosis. Currently there is no evidence-based therapeutic gold standard. Therefore, although it is challenging to design and perform an RCT in AMICS, the clinical need is high. Whereas it is acceptable to allow an innovative approach, such as the use of mechanical circulatory support, in a deadly disease like CS, the ultimate goal of an RCT is to confirm the validity of new therapeutic strategies with strong scientific evidence, and to appropriately assess the associated risk/benefit ratio. To succeed, it is extremely important to select the patients accurately. We have proposed several means to overcome the main challenges faced in such an endeavour: the choice of stringent inclusion criteria; an innovative approach to informed consent; randomization to an up-to-date medical therapy versus a strategy using early pAFP implantation; and a meaningful clinical endpoint not restricted to mortality. These are key features of an optimal RCT.

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References

[1] Kolte D, Khera S, Aronow WS, et al. Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. J Am Heart Assoc 2014;3:e000590.

[2] Goldberg RJ, Makam RC, Yarzebski J, McManus DD, Lessard D, Gore JM. Decade-Long Trends (2001—2011) in the Incidence and Hospital Death Rates Associated with the In-Hospital Development of Cardiogenic Shock after Acute Myocardial Infarction. Circ Cardiovasc Qual Outcomes 2016;9:117—25.

[3] Ko BS, Drakos SG, Welt FGP, Shah RU. Controversies and Challenges in the Management of ST-Elevation Myocardial Infarction Complicated by Cardiogenic Shock. Interv Cardiol Clin 2016;5:541—9.

[4] Truesdell AG, Tehrani B, Singh R, et al. ''Combat'' Approach to Cardiogenic Shock. Interv Cardiol 2018;13:81—6.

[5] Engstrom AE, Cocchieri R, Driessen AH, et al. The Impella 2.5 and 5.0 devices for ST-elevation myocardial infarction patients presenting with severe and profound cardiogenic shock: the

Academic Medical Center intensive care unit experience. Crit Care Med 2011;39:2072—9.
[6] Shah M, Patnaik S, Patel B, et al. Trends in mechanical circulatory support use and hospital mortality among patients with acute myocardial infarction and non-infarction related cardiogenic shock in the United States. Clin Res Cardiol 2018;107:287—303.
[7] Kapur NK, Paruchuri V, Urbano-Morales JA, et al. Mechanically unloading the left ventricle before coronary reperfusion reduces left ventricular wall stress and myocardial infarct size. Circulation 2013;128:328—36.
[8] Sun X, Li J, Zhao W, et al. Early Assistance With Left Ventricular Assist Device Limits Left Ventricular Remodeling After Acute Myocardial Infarction in a Swine Model. Artif Organs 2016;40:243—51.
[9] Cohen AT, Goto S, Schreiber K, Torp-Pedersen C. Why do we need observational studies of everyday patients in the real-life setting? Eur Heart J Suppl 2015;17:D2—8.
[10] Seyfarth M, Sibbing D, Bauer I, et al. A randomized clinical trial to evaluate the safety and efficacy of a percutaneous left ventricular assist device versus intra-aortic balloon pumping for treatment of cardiogenic shock caused by myocardial infarction. J Am Coll Cardiol 2008;52:1584—8.
[11] Bochaton T, Huot L, Elbaz M, et al. Mechanical circulatory support with the Impella(R) LP5.0 pump and an intra-aortic balloon pump for cardiogenic shock in acute myocardial infarction: The IMPELLA-STIC randomized study. Arch Cardiovasc Dis 2019 [pii: S1875-2136(19)30189-5].
[12] Ouweneel DM, Eriksen E, Sjauw KD, et al. Percutaneous Mechanical Circulatory Support Versus Intra-Aortic Balloon Pump in Cardiogenic Shock After Acute Myocardial Infarction. J Am Coll Cardiol 2017;69:278—87.
[13] Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129—200.
[14] Menon V, Slater JN, White HD, Sleeper LA, Cocke T, Hochman JS. Acute myocardial infarction complicated by systemic hypoperfusion without hypotension: report of the SHOCK trial registry. Am J Med 2000;108:374—80.
[15] Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. N Engl J Med 1999;341:625—34.
[16] Esposito ML, Kapur NK. Acute mechanical circulatory support for cardiogenic shock: the ''door to support'' time. F1000Res 2017;6:737.
[17] Jentzer JC, van Diepen S, Barsness GW, et al. Cardiogenic Shock Classification to Predict Mortality in the Cardiac Intensive Care Unit. J Am Coll Cardiol 2019;74:2117—28.
[18] Baran DA, Grines CL, Bailey S, et al. SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Society of Thoracic Surgeons (STS) in April 2019. Catheter Cardiovasc Interv 2019;94:29—37.
[19] Thiele H, Akin I, Sandri M, et al. PCI strategies in patients with acute myocardial infarction and cardiogenic shock. N Engl J Med 2017;377:2419—32.
[20] D'Arrigo S, Cacciola S, Dennis M, et al. Predictors of favourable outcome after in-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation: A systematic review and meta-analysis. Resuscitation 2017;121:62—70.
[21] Flaherty MP, Pant S, Patel SV, et al. Hemodynamic Support With a Microaxial Percutaneous Left Ventricular Assist Device (Impella) Protects Against Acute Kidney Injury in Patients Undergoing High-Risk Percutaneous Coronary Intervention. Circ Res 2017;120:692—700.
[22] Thiele H, Jobs A, Ouweneel DM, et al. Percutaneous short-term active mechanical support devices in cardiogenic shock: a systematic review and collaborative meta-analysis of randomized trials. Eur Heart J 2017;38:3523—31.
[23] Burkhoff D, Hemodynamic Support:. Science and Evaluation of the Assisted Circulation with Percutaneous Assist Devices. Interv Cardiol Clin 2013;2:407—16.
[24] Basir MB, Schreiber TL, Grines CL, et al. Effect of early initiation of mechanical circulatory support on survival in cardiogenic shock. Am J Cardiol 2017;119:845—51.
[25] Schrage B, Ibrahim K, Loehn T, et al. Impella support for acute myocardial infarction complicated by cardiogenic shock. Circulation 2019;139:1249—58.
[26] Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet 2014;384:1849—58.
[27] Burkhoff D, Cohen H, Brunckhorst C, O'Neill WW. TandemHeart Investigators Group. A randomized multicenter clinical study to evaluate the safety and efficacy of the TandemHeart percutaneous ventricular assist device versus conventional therapy with intraaortic balloon pumping for treatment of cardiogenic shock. Am Heart J 2006;152 [469 e1-8].
[28] Hall SA, Uriel N, Carey SA, et al. Use of a percutaneous temporary circulatory support device as a bridge to decision during acute decompensation of advanced heart failure. J Heart Lung Transplant 2018;37:100—6.
[29] Helleu B, Auffret V, Bedossa M, et al. Current indications for the intra-aortic balloon pump: The CP-GARO registry. Arch Cardiovasc Dis 2018;111:739—48.
[30] Sandhu A, McCoy LA, Negi SI, et al. Use of mechanical circulatory support in patients undergoing percutaneous coronary intervention: insights from the National Cardiovascular Data Registry. Circulation 2015;132:1243—51.
[31] Na SJ, Chung CR, Jeon K, et al. Association between presence of a cardiac intensivist and mortality in an adult cardiac care unit. J Am Coll Cardiol 2016;68:2637—48.
[32] Shaefi S, O'Gara B, Kociol RD, et al. Effect of cardiogenic shock hospital volume on mortality in patients with cardiogenic shock. J Am Heart Assoc 2015;4:e001462.
[33] Tehrani BN, Truesdell AG, Sherwood MW, et al. Standardized Team-Based Care for Cardiogenic Shock. J Am Coll Cardiol 2019;73:1659—69.
[34] Combes A, Hajage D, Capellier G, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. N Engl J Med 2018;378:1965—75.
[35] O'Neill WW, Grines C, Schreiber T, et al. Analysis of outcomes for 15,259 US patients with acute myocardial infarction cardiogenic shock (AMICS) supported with the Impella device. Am Heart J 2018;202:33—8.
[36] Vetrovec GW, Anderson M, Schreiber T, et al. The cVAD registry for percutaneous temporary hemodynamic support: A prospective registry of Impella mechanical circulatory support use in high-risk PCI, cardiogenic shock, and decompensated heart failure. Am Heart J 2018;199:115—21.
[37] Jensen PB, Kann SH, Veien KT, et al. Single-centre experience with the Impella CP, 5.0 and RP in 109 consecutive patients with profound cardiogenic shock. Eur Heart J Acute Cardiovasc Care 2018;7:53—61.
[38] Basir MB, Schreiber T, Dixon S, et al. Feasibility of early mechanical circulatory support in acute myocardial infarction complicated by cardiogenic shock: The Detroit cardiogenic shock initiative. Catheter Cardiovasc Interv 2018;91:454—61.

[39] Flaherty MP, Khan AR, O'Neill WW. Early Initiation of Impella in Acute Myocardial Infarction Complicated by Cardiogenic Shock Improves Survival: A Meta-Analysis. JACC Cardiovasc Interv 2017;10:1805—6.
[40] Bonello L, Delmas C, Schurtz G, et al. Mechanical circulatory support in patients with cardiogenic shock in intensive care units: A position paper of the ''Unite de Soins Intensifs de Cardiologie'' group of the French Society of Cardiology, endorsed by the ''Groupe Atherome et Cardiologie Interventionnelle'' of the French Society of Cardiology. Arch Cardiovasc Dis 2018;111:601—12.
[41] Subramaniam AV, Barsness GW, Vallabhajosyula S, Vallabhajosyula S. Complications of Temporary Percutaneous Mechanical Circulatory Support for Cardiogenic Shock: An Appraisal of Contemporary Literature. Cardiol Ther 2019;8:211—28.
[42] Lauten A, Engstrom AE, Jung C, et al. Percutaneous left-ventricular support with the Impella-2.5-assist device in acute cardiogenic shock: results of the Impella-EUROSHOCK-registry. Circ Heart Fail 2013;6:23—30.