Rationale and design of the ULYSS trial: A randomized multicenter evaluation of the efficacy of early Impella CP implantation in acute coronary syndrome complicated by cardiogenic shock

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Highlights

- Prognosis of acute myocardial infarction with cardiogenic shock remains poor.
- Acute MCS may improve outcomes, but observational data are controversial.
- The ULYSS trial is a multicentric randomized open-label clinical trial.
- Pre-PCI IMPELLA CP implantation will be compared to standard of care.
- A composite endpoint will assess death, need to escalate to ECMO, heart transplantation or LVAD at 30-day.

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Abstract (247 words)

Despite 20 years of improvement in acute coronary syndromes care, patients with acute myocardial infarction complicated by cardiogenic shock (AMICS) remains a major clinical challenge with a stable incidence and mortality. While intra-aortic balloon pump (IABP) did not meet its expectations, percutaneous mechanical circulatory supports (pMCS) with higher hemodynamic support, large availability and quick implementation may improve AMICS prognosis by enabling early hemodynamic stabilization and unloading. Both interventional and observational studies suggested a clinical benefit in selected patients of the IMPELLA® CP device within in a well-defined therapeutic strategy. While promising, these preliminary results are challenged by others suggesting a higher rate of complications and possible poorer outcome. Given these conflicting data and its high cost, a randomized clinical trial is warranted to delineate the benefits and risks of this new therapeutic strategy. The ULYSS trial is a prospective randomized open label, 2 parallel multicenter clinical trial that plans to enroll patients with AMICS for whom an emergent percutaneous coronary intervention (PCI) is intended. Patients will be randomized to an experimental therapeutic strategy with pre-PCI implantation of an IMPELLA® CP device on top of standard medical therapy or to a control group undergoing PCI and standard medical therapy. The primary objective of this study is to compare the efficacy of this experimental strategy by a composite endpoint of death, need to escalate to ECMO, long-term left ventricular assist device or heart transplantation at 1 month. Among secondary objectives one-year efficacy, safety and cost effectiveness will be assessed.

Key words

Acute coronary syndrome, percutaneous coronary intervention, cardiogenic shock, mechanical circulatory support, RCT, prognosis.

Abbreviations

ACS, acute coronary syndrome; AMI, acute myocardial infarction; AMICS, acute myocardial infarction complicated by cardiogenic shock; BNP, brain natriuretic peptide; CI, cardiac index; NtproBNP, N-terminal pro BNP; CS, cardiogenic shock; ECMO, veno-arterial membrane oxygenation membrane; IABP, intra-aortic balloon pump; ICU, intensive care unit; LVAD, left ventricular assist device; MCS, mechanical circulatory support; pMCS, percutaneous mechanical circulatory support; PCI, percutaneous coronary intervention; QALY, Quality adjusted life year; SBP, systolic blood pressure; RHC, right heart catheterization; ROSC, return of spontaneous circulation; SCAI, society for cardiovascular angiography and interventions; ScVO2, venous oxygen saturation in the superior vena cava

INTRODUCTION

Despite improvements in the care of patients with an acute myocardial infarction complicated by cardiogenic shock (AMICS), the mortality rate remains around 50% at 1 month [1]. In addition to early culprit revascularization with percutaneous coronary intervention (PCI), the current guidelines suggests medical therapy with inotropic support and vasopressor to restore cardiac output and adequate organ perfusion with a low level of evidence (class IIbC) [1, 2]. In fact, hemodynamic stabilization is critical to prevent multi-organ dysfunction and death. Most of the current interventions to stabilize the hemodynamic in AMICS have a low level of evidence, only backed by expert's consensus, because of the limited number of randomized clinical trials [3]. In addition, catecholamines, which are recommended in this clinical setting, may be deleterious has they increase myocardial oxygen consumption and may thus favor a vicious circle [4]. Intra-aortic balloon pump (IABP) was the first device developed to support hemodynamics in AMICS. Nevertheless, after years of use, the IABP Shock 2 trial demonstrated the lack of benefit of this device [5]. Its use is limited to AMI patients with mechanical complications in the guidelines (class IIb level of evidence C) [6]. An intravascular microaxial blood pump, the IMPELLA® CP® device, was developed as a short-term percutaneous mechanical circulatory support (pMCS) for AMICS patients. It provides a sustained hemodynamic support compared to IABP [7, 8] and has several potential advantages in AMICS patients including a large availability and a quick percutaneous implementation in the catheterization laboratory allowing a reduction of the "time to support". In addition, it unloads the left ventricle (LV) favoring recovery and potentially limiting infarct size [8]. From a clinical standpoint, observational data suggest that in selected patients with an ACS complicated by CS the use of IMPELLA® devices could reduce mortality [9–11]. In addition, the care of acute coronary syndromes is based on networks mainly dependent on centers without ECMO in France. Therefore, the IMPELLA® device would provide

physicians with ability to assist a larger share of patients and dramatically reduce time to support [12]. However, despite encouraging results, no randomized controlled trial has yet confirmed its benefits and adequately assessed its safety [13]. Because pMCS devices are associated with specific complications and are costly, obtaining strong scientific evidences is of major interest for patients, physicians and health authorities [3, 14, 15]. Therefore, randomized data are highly warranted to settle this issue.

We designed the ULYSS trial to evaluate the efficacy of a therapeutic strategy of early implantation of the IMPELLA® CP device before PCI compared to optimal medical care. This will be assessed by a composite endpoint including all cause death, need to escalate to ECMO support and the need of heart transplant or of long-term LVAD in AMICS. Safety and economic impact will also be evaluated.

METHOD

Study design

The ULYSS study is a multicenter, randomized, controlled, open-label, prospective and two-parallel group trial. The study design is registered at clinicaltrials.gov (database: NCT05366452). This trial will be performed in 15 shock centers in France which have a shock team available 24/24 7/7. The study is sponsored and funded by the Programme Hospitalier de Recherche Clinique (PHRC 2019) and is an independent study promoted by Assistance Publique-Hôpitaux de Marseille. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Patients

Patients will be eligible if the diagnosis of AMICS is made and if an invasive strategy is intended. Both ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) are eligible. The inclusion and non-inclusion criteria are detailed in **Table 1** including the definition of CS used. The present study will focus of patients with stage C and D CS according to the SCAI classification [16].

Once a patient enters the emergency, intensive or cardiology care unit, his/her information is collected as part of the routine care and will be reviewed to determine eligibility for enrollment. These include a physical exam, 12 lead electrocardiograms (ECG), cardiac biomarker analysis (troponin and Ck-Mb) and all means considered necessary for diagnosis of ACS and CS.

A transthoracic echography is required to exclude mechanical complications and non-inclusion criteria. Randomization will be made after an informed consent is signed.

After delivery of oral information regarding the study (objectives, schedule, benefits, risks, etc.), the written consent will be collected. If a patient is unable to consent, a family member's consent will be sleeked. When neither the patient nor a family member can consent, an emergency consent could be used. When a patient is included in these conditions, his consent will be asked as soon as possible (Article L. 1122-1-2 of the French Public Health Code). Any patient wishing to withdraw consent during the study will be excluded.

Subjects will then be randomized 1:1 to one of the 2 groups below (**Figure 1**). In the control group, patients will receive inotropes associated or not with vasopressors as soon as possible according to the attached protocol and based on the current guidelines (**Supplementary material**). The aim will be to restore a mean arterial pressure of 65 mmHg. Emergent culprit revascularization will also be performed. In the experimental group, the IMPELLA® CP device will be implanted before revascularization, on top of usual care. Once IMPELLA® CP is functioning, emergent culprit lesion PCI will be performed. Support with IMPELLA® CP

for more than 24 hours is strongly encouraged. Inotropes and vasopressors should be weaned first and as soon as possible after IMPELLA® implantation (**Supplementary material**).

A dedicated protocol will ensure that management is similar between centers and in both groups (**Supplementary material**). The shock team of each site (interventionalist, heart failure specialist and intensivist) will oversee all therapeutic decisions.

The only difference between the two groups of patients will be the implantation (or not) of the IMPELLA® CP device before PCI. All patients will be monitored in Cardiovascular or general Intensive Care Units (CCU or ICU), depending on the shock team decision and local organization.

Randomization

The list of randomizations will be established before the implementation of the study with a 1:1 allocation ratio. A computer-generated randomized list will be drawn up using a permuted block design (stratified on center). Each center will have a specific list. A randomization sequence will be generated using R software (blockrand package). Block size will randomly vary among 2, 4, and 6 so that it will prevent to predict the next assignment.

Percutaneous coronary intervention and antithrombotic therapy

PCI of the culprit lesion will be performed as soon as possible according to the guidelines [17]. Non culprit lesions should be treated during a staged procedure. The patients will receive usual care including aspirin therapy and anticoagulation according to guidelines and center's protocols after PCI [17]. P2Y12-ADP receptor antagonists will be given as loading dose as soon as possible. The choice of anticoagulant, the use of glycoprotein 2b/3a inhibitors and the type of P2Y12-ADP receptor antagonist will be left at physician's decision between drugs listed in the guidelines [17]. Prasugrel and Ticagrelor are preferred over Clopidogrel.

The recommended duration of dual antiplatelet therapy will be of 12 months but may vary according to patient thrombotic and bleeding risks based on guidelines [17].

IMPELLA® CP implantation

Implantation of the IMPELLA® CP will be performed using the femoral route in all patients. Echo-guided puncture to gain access for IMPELLA® CP and a local angiography to check the feasibility of device implantation will be encouraged. The implantation will follow the gold standard after obtaining an ACT >250 s [18]. As soon as the device is in place it will be started. Sub-clavian or other arterial access could be seeked if required at the discretion of the physician. Prolonged curative unfractionated heparin infusion is required in the experimental group as long as the IMPELLA® device is in place according to manufacturer's instructions [19]. Specific IMPELLA® management and monitoring protocols are described in **Supplementary Material**.

Other care management

All patients will receive recommended derived medical care according to ESC guidelines [1, 6, 17]. Following PCI there will be no difference between the 2 groups in the therapeutic strategy and medical care. The common medications prescribed for CS and ACS subjects are described below.

Inotropes/Vasopressors

The gold standard for inotrope is Dobutamine. Epinephrine is not allowed except for cardiac arrest indication. Norepinephrine is preferred to restore mean arterial pressure and quickly implemented in case of persistent hypotension despite Dobutamine and fluid management. The shock team can decide differently at any time if necessary. The administration of these drugs will be based on the protocol described in **Supplementary Material** which is derived

from the guidelines and the most recent literature to allow optimal care and homogenous care between centers.

Oxygen therapy will be provided in order to maintain an arterial saturation of oxygen above 90% using any means including invasive ventilation when required [6].

Monitoring of patients in both groups will be performed according to the guidelines and according to the shock team needs [19]. It will include central venous line (preferentially on superior vena cava territory if possible), invasive arterial monitoring, transthoracic echocardiography, and repeated blood gases with lactates measurements.

Treatment at discharge

Introduction and optimization of drug therapy according to the guidelines of ACS and heart failure will be encouraged [6, 20]. The use of all concomitant medications and medications at discharge will be recorded on the eCRF and summarized by treatment cohort.

Follow-up and study endpoints

The primary endpoint is composite and includes death from all causes, escalation to ECMO, heart transplant and long-term LVAD at 1 month.

First, patients could be escalated to VA-ECMO whatever the study group, under one of the 3 following conditions: refractory cardiogenic shock, uncontrolled lethal arrhythmia, and refractory cardiac arrest (**Table 2**). This decision is left to the shock team of each center based on patients' status. Secondly, patients can be put on the heart transplant list or can receive heart transplant if they fulfilled 2 conditions: heart team decides that they need a transplant AND they fulfill the current criteria of the *Agence de la Biomédecine. Thirdly, l*ong-term LVAD implantation is based on heart team's decision related to lack of recovery based on International Guidelines [6].

A clinical follow-up will be made by local investigator at 30-day and at 1-year during dedicated consultation with physical exam and TTE.

The date of the events' occurrence will be collected, and the delay will be calculated from the randomization day.

Secondary endpoints include efficacy, safety and economic endpoints which are listed in **Table 3**. A one-year follow-up will evaluate long-term efficacy and quality-of-life (EQ5D questionnaire). Safety will be assessed during hospital stay, at one month and 1 year and will include bleeding and vascular events. Among secondary endpoints, a cost effectiveness analysis will also be performed, in which effectiveness will be expressed in terms of quality-adjusted life years (QALYs).

Institutional Review Board

An independent Institutional Review Board will be constituted before the beginning of the research in accordance with the French law. It will include a cardiologist, an emergency physician, an intensivist and a methodologist. It will have a consultative role on the general organization of the research, on the decision-making for which an independent advice is desirable (premature stop of the research, premature stop of participation of a subject).

An independent Clinical Endpoints Committee (CEC), blinded to the treatment, will adjudicate all events. Primary analyses will be conducted on CEC-adjudicated endpoints.

Moreover, safety monitoring will be conducted under the auspices of an independent, external data monitoring committee (DMC) assigned to this study.

Statistical aspects

Sample size calculation

The rate of complications in AMICS patients without prolonged cardiac arrest is of 65 % at 1 month with usual medical care [21]). It includes 45 % mortality, 15 % need for MCS and 5 % need for heart transplant or LVAD [3]. The IMPELLA® CP device delivers up to 3.0 to 3.5 l/min of blood flow thus significantly improving the hemodynamic parameters of patients with CS and reducing infarct size [8]. In the US registries, pre-PCI implantation of the IMPELLA® CP was associated with a 50% reduction in mortality [7, 9].This device is likely to reduce by half the need to escalate to ECMO, the need of heart transplant or of long-term LVAD. Overall, the implantation of IMPELLA® CP should reduce the rate of primary endpoint by 30% in these patients. With a bilateral alpha risk of 5% and a power of 80%, 96 patients by group are required in order to show a significant difference between 65 and 45% of the 1-month incidence of the primary end-point. In addition, we will perform an interim analysis when 50% of patients will be randomized and will have completed the 1-month follow-up. Therefore, 99 patients are required (according to O'Brien-Fleming method: interim boundary to stop the trial for efficacy: difference higher than 28%; interim boundary to stop the trial for futility: difference lower than 7%). Because of the potential loss to follow-up and loss of balance in the randomization process due to the multicentric nature of the study, we will include 102 patients per group, ie 204 patients in total**.**

The design allows adapting the sample size in the case of a lower than anticipated mortality. In such case, enrollment will continue until 100 events have occurred.

In accordance with the selection criteria and the recruitment capacity of the participating centers, we estimated that the inclusion period will be of 36 months. The maximal duration of participation for each patient is a 12-months period.

Description of statistical methods to be used.

The data will be analyzed using R software version 4.3.0 or later version. All tests will be two-sided. Statistical significance will be defined as $p<0.05$. The methodology will be based on the Consolidated Standards of Reporting Trials Statement (CONSORT, www.consort-statement.org/consort-statement). Statistical analysis will be reported using CONSORT guidelines. Patients will be assigned to the arm they are randomized into.

For efficacy endpoints, all patients will be analyzed according to the intention-to-treat principle (ITT). As a sensitivity analysis, a per-protocol analysis will also be performed.
For safety endpoints, patients will be analyzed according to the per-protocol principle. As a sensitivity analysis, an ITT method will also be performed.

Efficacy analysis
The incidence rate over the first month period of the primary efficacy composite endpoint (death, need for ECMO, need for long-term LVAD and/or heart transplant) will be estimated with a 95% confidence interval (95% CI) in each study arm. We will use time-to-event approach, considering both the occurrence of the primary endpoint and the time to this occurrence (or censoring).

Kaplan-Meier method will be used for the estimation of the incidence rate and the Logrank test for the comparison between study arms. A Cox proportional hazards regression model will be fitted to estimate the hazard ratio (with a 95%CI), expressing the impact of the intervention on the time-to-occurrence of the endpoint over the first month period. As the center will be used as a stratification factor in the randomization process, il will be considered in the model by statistical adjustment. In case of a loss of balance in the randomization process, multivariate analyses taken into account more factors will be considered for the

above-mentioned analyses, by adjusting the regression models on the data for which an imbalance would have been observed.

As a sensitivity analysis, the first month cumulative incidence rate will be estimated with its 95%CI in each study arm. It will then be compared using chi-square test if valid (Fisher's test otherwise). A logistic regression model will be fitted to estimate the odds ratio (with its 95%CI) expressing the impact of the intervention on the first month occurrence of the endpoint.

As a secondary analysis, to consider the different clinical relevance and severity of the components of the compositive primary endpoint, a win-ratio analysis will be performed. Unpaired analysis of the hierarchical components of the primary endpoint will be made at 30-day: (1) all-cause death, (2) need LVAD or heart transplantation and (3) need implementation to ECMO. Win-ratio will be estimated with its 95% confidence interval (95%CI) and its associated p-value [22].

For the cost-effectiveness analysis, the number of QALYs will be computed from data on survival and repeated measures of health related QoL. Cost resources will be valued using data from the National Healthcare system and hospital databases. An incremental cost-effectiveness ratio (ICER) will be calculated. The statistical uncertainty surrounding the ICER will be captured by both deterministic and probabilistic analyses, using, among others, simulation methods such as non-parametric bootstrap methods. Cost-effectiveness acceptability curves will also be provided.

Recruitment of the ULYSS trial

Recruitment for the ULYSS trial started in December 2022. Due to administrative regulation, 6 of the 15 planned investigators centers are currently opened. As of June 2023, 8 patients have been recruited in 2 centers. With an increasing number of sites opening in the next

weeks and months, the projected recruitment rate will increase. We anticipate completion of recruitment within 36 months.

Discussion

Cardiogenic shock management limits

AMICS remains a major clinical challenge with a high mortality rate [1, 21]. Standard approaches are based on catecholamine use for hemodynamic stabilization but they may be deleterious and associated with poor outcomes especially for epinephrine [4]. Mechanical circulatory supports have therefore been proposed and short-term MCS (especially ECMO) are proposed for selected patients deteriorating under medical therapy (stage D SCAI) although no randomized trials support their use [2, 6, 19]. However, ECMO is associated with a high rate of complications, has a limited availability and require a complex monitoring in specialized units [23]. In addition, it provides a retrograde flow which may cause additional LV injury and favors pulmonary edema [19]. More, its use in left ventricular predominant CS was shown to be associated with a 3-fold increase in 90-day mortality in a recent large retrospective study reinforcing its potential deleterious effect in case of AMICS [24]. And recently, the ECMO-CS study failed to show any benefit of ECMO compared to standard therapy in 122 patients with severe or deteriorating CS [25].

Place for pMCS in AMICS

More recently, the IMPELLA® CP device has been proposed in AMICS because of several theorical advantages over ECMO: it provides a sustained continuous blood flow improving systemic and coronary perfusion, unload the left ventricle, reduce myocardial infarction size and prevent progressive systemic inflammatory response syndrome [18, 26]. In addition, it is widely available and can be quickly implemented in cath-labs thus increasing the number of

eligible patients and reducing the time to support. Observational studies suggest that in selected patients with AMICS its implantation before the PCI may reduce mortality [10, 11]. It is implemented in the National Cardiogenic Shock Initiative (NCSI) consortium in US which build a very effective protocol of care to adequately select patients and provide timely hemodynamic support which translate into a continuous improvement in outcomes [9, 12]. Based on the above-mentioned properties, it is likely to reduce the need for ECMO, LVAD and heart transplant in AMICS patients. Finally, providing to center without ECMO a MCS which could be quickly implemented in this complex clinical situation would increase the availability of MCS, reduce time to therapy and will therefore increase the number of patients likely to benefit from these devices thus improving the clinical outcome. However, a controversy remains because of the lack of randomized clinical trials demonstrating the superiority of this strategy, potential safety issues and its cost [27, 28].

Patients' selection and CS protocols

One critical point to ensure feasibility of such a trial is the selection of patients [29]. Accurate selection is required to include patients who are in stage C or D of the SCAI classification. In higher stages of CS (stage E) the device may not provide sufficient output and the outcome may be more related to multi-organ dysfunction and refractory CS [5, 21]. In addition, the IMPRESS trial demonstrated that in patients with CS following cardiac arrest the IMPELLA® device did not improve outcome since most patients died of anoxic encephalopathy [13]. Otherwise, in the lower stage (stage B), the risk benefit ratio may not be favorable since the reported mortality rate in the literature for stage A and B is low and lower than potential severe associated complications. Finally, only patients with a high probability of heart function recovery or eligible for a long-term project should be included.

Equipoise is challenging in the context of AMICS. However, the literature remains controversial for the early use of MCS in CS with some suggesting overall improved outcome

with early IMPELLA® or ECMO [9, 30] while other observational studies observe harm [28]. In addition, although the current therapy in AMICS remains based on a low level of evidence, the proposed medical therapy in the control group will be a standard protocol of care which will be consistent with that of the experimental group thus enabling a fair comparison and homogenous care between centers.

Limits of ongoing studies

Several attempts at performing such trial have failed for various reasons [29]. The DanGerShock trial that began over 10 years ago (start in July 2012), has just finished its inclusions, and is expected to be released in the coming months, but presents some important difference with the ULYSS trial (**Supplementary Table 1)**. First, the DanGerShock trial permits only the inclusion of STEMI patients explaining probably in part its slow enrolment rate. A recent analysis of a large multicentric database of CS estimated that only 24.4% of AMICS referred in tertiary centers were eligible for the DanGerShock trial (versus 55.3% for IABP-SHOCK 2 trial). Second, in the DanGerShock trial the device can be implanted within 12 hours after the PCI and until 36 hours after STEMI while the benefit of the IMPELLA® was shown to be dependent on the early implant timing [11, 14]. Third, in the ULYSS trial patients with severe shock will not be included to prevent futile use of MCS unlike in the DanGerShock where patients already included were severe shock (LVEF 20%, lactate 5.5mmol/l, catecholamine infusion 94%, 86% mechanical ventilation and renal replacement therapy 34%) decreasing the ability of the trial to show any benefit of the IMPELLA®. Fourth, in the DanGerShock trial, patients remaining unstable will be escalated to ECMO in the control group but not in the interventional arm (only escalation to IMPELLA® 5.0, LVAD or heart transplantation is allowed) limiting the comparability of the groups. Finally, the 2 trials have different endpoints: all-cause death rate at 180-day for the DanGerShock trial and a composite primary endpoint at 30-day including mortality, escalation to ECMO,

transplant and LVAD for the ULYSS trial. The consideration of the absence of myocardial recovery as a component of the primary endpoint in the ULYSS trial (need for LVAD or heart transplantation) is particularly relevant to fully cover the supposed benefit of the IMPELLA® device: to prevent or correct multiple organ failure and to promote myocardial recovery. In addition, the adjunction of the IMPELLA® CP failure (need for ECMO escalation) in the composite endpoint is of almost importance from a clinical and medico-economic perspective for patients and healthcare system.

Likewise, the future RECOVER IV trial (NCT05506449) will face some of the limitations of the DanGerShock study (**Supplementary Table 1**) with inclusion of only STEMI patients and the use of different escalations' strategies between interventional (Impella 5.5 and/or RP) and control groups (any others acute MCS). Main strengths of this study are the pre-PCI implantation of the IMPELLA® device, the systematic realization of a right heart catheterization (RHC) (before or immediately after PCI) and a large multicenter enrollment of 506 patients in US. Main limitations are the absence of standardization of AMICS management in the control group and a non-academic sponsor (Abiomed®). The Study start is estimated on 2023-10-01 with a completion date estimated on 2026-04-30 which seems a very optimistic based on the size of the population needed.

Challenges and limitations

First, one of the main challenges is the ability of the centers to recruit patients in this clinical setting who fulfil to the inclusion and non-inclusion criteria. The active participation of the CCU network from the Emergency and Acute Cardiovascular Care Working Group of the French Society of Cardiology, and the possibility to include STEMI and non-STEMI patients in the first 24 hours of the ACS, will facilitate the enrollment of patients in a timely manner. The absence of systematic RHC will not allow us a fine hemodynamic analysis of the effects of the IMPELLA® device, nor the consideration of RHC parameters in our

inclusion/exclusion criteria nor in our escalation criteria. Despite a revival of the place of RHC in the management of CS due to its positive association with short-term outcomes in recent observational studies [31], its use remains controversial, and little used in France. We decided not to complicate our protocol about the practices in force in the investigating centers so as not to limit inclusions.

Second, while some might consider the use of a composite endpoint as having less value than the use of all-cause mortality, a multidisciplinary international group has on the contrary recently highlighted the interest of this type of approach for CS studies [32]. Experts proposed the utilization of three alternative continuous hierarchical composite endpoints for future AMICS trials: the rate of patients alive and organ-support free (as used in our pragmatic trial), the global rank score, or the number of days alive and out of hospital. This approach should permit the estimation of a precise average treatment effect between study arms, the assessment of heterogeneity of treatment effect, and to achieve lower sample size needs. All these considerations should favor the realization of AMICS studies and their interpretations explaining its frequent use in ongoing and future CS studies (LevoHeartShock (NCT04020263), REVERSE (NCT03431467), ANCHOR (NCT04184635) or ALTSHOCK2 trial (NCT04369573)).

Third, the open nature of the trial is a limitation, but the blind adjudication committee will tend to reduce this bias. Furthermore the present study is an open study without a sham group. This could also lead to potential limitations despite stringent protocol of care and of treatment escalation. Finally, inclusion criteria and into a RCT may tend to select lower risk patients than anticipated.

Conclusion

The ULYSS trial is a prospective multicenter randomized controlled open label study comparing the efficacy of the early implantation of the IMPELLA® CP device in CS complicating AMI to standard of care. The primary endpoint will be a composite of death, escalation to ECMO, need for LVAD or heart transplantation at 1 month. The aim of trial is to determine the optimal therapeutic strategy in AMICS.

Conflict of interest

CD report consulting and lectures fees for ABIOMED

LB report consulting and lectures fees for ABIOMED

GS report lectures fees for ABIOMED

Other authors have nothing to report.

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FIGURES LEGENDS

Figure 1: The ULYSS trial design
ACS, acute coronary syndrome; AMICS, acute myocardial infarction associated cardiogenic shock; ECMO, venoarterial extracorporeal membrane oxygenation; LVAD, left ventricular assist devive; PCI, percutaneous coronary intervention.

TABLES

Table 1: Inclusion and non-inclusion criteria of the ULYSS trial
ACS, acute coronary syndrome; BNP, brain natriuretic peptide; CI, cardiac index; NtproBNP, CS, cardiogenic shock; N-terminal pro BNP; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; ROSC, return of spontaneous circulation; SCAI, society for cardiovascular angiography and interventions; ScVO2, venous oxygen saturation in the superior vena cava.

Table 2: Escalation criteria to VA-ECMO in the ULYSS trial
IV, intra-venous; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VTI, velocity time integral

Table 3: Secondary endpoint of the ULYSS trial
BARC, Bleeding Academic Research Consortium; ECMO, veno-arterial membrane oxygenation membrane; EQ5D, EuroQol Group; QALY, quality-adjusted life year; ICU, intensive care unit; LVAD, left ventricular assist device; RBC, red blood cells.

Figure 1: ULYSS design

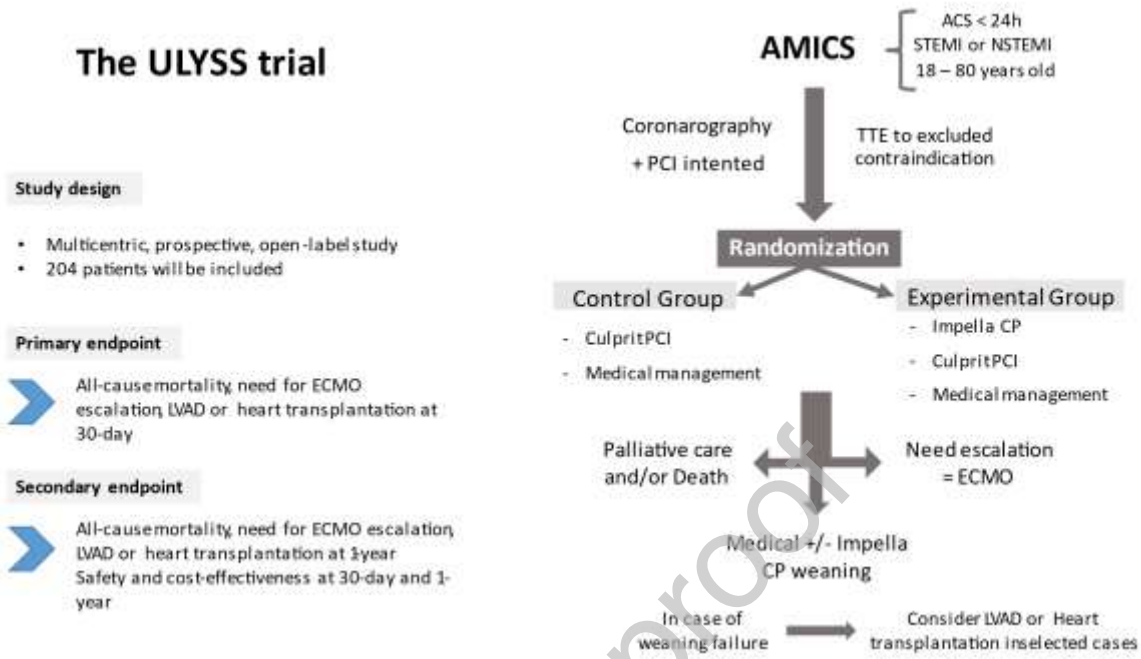

Table 1: Inclusion and non-inclusion criteria of the ULYSS trial.

Inclusion Criteria

The eligible subjects must meet all the following criteria:

- Age between 18 and 80 years old.
- ACS ≤ 24 hours.
- Cardiogenic shock defined by:
    - At least one criteria of low cardiac output defined by
        - SBP ≤ 90 mmHg or the need to use inotropes/vasopressors in order to obtain SBP > 90 mmHg
        - CI ≤ 2.2L/min/m2
    - At least one criteria of left overload defined by
        - Clinical (Killip class ≥ 2),
        - Biological (NtproBNP > 900pg/ml or BNP > 400pg/ml),
        - Radiological
        - Non-invasive or invasive hemodynamic evaluation
    - At least one criterion of malperfusion defined by
        - Clinical (skin mottling, oliguria ≤ 0.5ml/min/kg, cold/clammy skin and extremities...)
        - Biological approach (arterial lactate ≥ 2mmol/L, ScVO2 < 60%)
- Stage C or D of the SCAI classification of CS
- Revascularization by PCI intended after coronary angiography.
- Patient with a high probability of heart function recovery or eligible for an advanced heart failure therapy namely heart transplantation and/or ventricular assist device
- Lack of significant femoral artery stenosis or other local contra-indication to a 14 Fr sheath.
- Signed informed consent (patient and/or family/relative) or emergency procedure.
- Subject affiliated to or beneficiary of a social security system.

Non-inclusion criteria

- Persons referred in articles L.1121-5 to L.1121-8 and L.1122-2 of the French Public Health Code:
    - Pregnant or breastfeeding woman
    - Person deprived of liberty for judicial or administrative decision
    - Person under psychiatric care
    - Adult person under legal protection (any form of public guardianship)
- Subject not agreeing to participate.
- Onset of shock >24 hours
- Contra-indication to antiplatelet or anticoagulant therapy
    - History of heparin induced thrombocytopenia.
    - Bleeding diathesis
- Anoxic brain injury / Cerebral deficit with fixed dilated pupils or irreversible neurological pathology
- Unwitnessed out of hospital cardiac arrest or any cardiac arrest with ROSC >10 min, any low flow above 1 minute and a Glasgow>8 on arrival
- Contra-indication to Impella device:
    - Isolated right ventricular failure*.
    - Left ventricle thrombus.
    - Mechanical aortic valve.
- Mechanical complication of myocardial infarction
- Life expectancy < 1 year

* Isolated right ventricular (RV) failure is defined as a RV systolic and/or diastolic dysfunction defined by the association of clinical and/or echocardiographic and/or biological and/or invasive hemodynamic signs of right heart failure without severe left ventricular dysfunction (See supplementary material).

ACS, acute coronary syndrome; BNP, brain natriuretic peptide; CI, cardiac index; CS, cardiogenic shock; Nt-proBNP, N-terminal brain natriuretic peptide; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; ROSC, return of spontaneous circulation; SCAI, society for cardiovascular angiography and interventions; ScVO2, venous oxygen saturation in the superior vena cava.

Table 2: Escalation criteria to VA-ECMO in the ULYSS trial.

Patient management should be escalated if at least one of the following situations is fulfilled.

1. Refractory cardiogenic shock defined as
   - Cardiac index < 2 l/min/m² or aortic VTI <6 cm
     AND
   - Assessment and correction of hypovolemia
     AND
   - Dobutamine ≥ 15 µg/kg/min + norepinephrine ≥ 0.45 µg/kg/min OR norepinephrine ≥ 0.45 µg/kg/min
     AND
   - Serum lactate > 4 mmol/L or serum lactate increased > 25% in the last 6 hours despite optimal medical management.
2. Uncontrolled lethal arrhythmia despite
   - IV loading dose of amiodarone (5mg/kg)
     AND
   - IV xylocaine slow intra-venous infusion dose (1mg/kg)
3. Refractory cardiac arrest

IV, intra-venous; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VTI, velocity time integral

Table 3: Secondary endpoints collected in the ULYSS trial

		In-hospital	At discharge	At 1-month	At 1-year
Efficacy endpoints					
	All-cause death		X	X	X
	ECMO implementation		X	X	X
	LVAD implantation		X	X	X
	Heart transplantation		X	X	X
	Duration of catecholamines use	X			
	Lactate clearance during the first 24 hours	X			
	Area under the curve of CK release during the first 4 days	X			
	Length of in-hospital stay		X		
	Length of stay in ICU		X		
	Myocardial infarctions		X	X	X
	Strokes		X	X	X
	Urgent revascularizations		X	X	X
	CV deaths		X	X	X
	Procedural success (hospital discharge only)		X		
	Renal replacement therapies	X	X	X	X
	LVEF			X	X
	QoL (EQ5D questionnaire)			X	X
Safety endpoints					
	Rate of serious adverse events (urgent vascular surgery, severe bleedings, transfusion, emboli).		X	X	X
	Rate of BARC bleedings ≥3		X	X	X
	Number of major vascular complications according to the VARC2 definition		X	X	X
	Hemostasis parameters, particularly hemolysis		X	X	
	Requirement for transfusion (total number of RBC)		X	X	
	Number of systemic embolisms;		X	X	
	All others adverse events		X		
Economic endpoints					
	Total health care resource used at one year				X
	Assessment of the patients' utility value for health states using the EQ5D-5L	X			X
	One year cost-utility analysis: calculated by an incremental cost-utility ratio in terms of costs per additional quality-adjusted life year (QALY).				X

BARC, Bleeding Academic Research Consortium; ECMO, veno-arterial membrane oxygenation membrane; EQ5D, EuroQol Group; QALY, quality-adjusted life year; ICU, intensive care unit; LVAD, left ventricular assist device; RBC, red blood cells, VARC-2, Valve Academic Research Consortium-2.