EuroIntervention 2021;16:e1227-e1236 published online October 2020 ■ published online e-edition February 2021

Veno-arterial extracorporeal membrane oxygenation (ECMO) in patients with cardiogenic shock: rationale and design of the randomised, multicentre, open-label EURO SHOCK trial

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-01076

KEYWORDS

- ACS/NSTE-ACS
- acute heart failure
- cardiogenic shock
- depressed left ventricular function

Abstract

Aims: Cardiogenic shock (CGS) occurs in 6-10% of patients with acute coronary syndromes (ACS). Mortality has fallen over time from 80% to approximately 50% consequent on acute revascularisation but has plateaued since the 1990s. Once established, patients with CGS develop adverse compensatory mechanisms that contribute to the downward spiral towards death, which becomes difficult to reverse. We aimed to test in a robust, prospective, randomised controlled trial whether early support with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides clinical benefit by improving mortality and morbidity.

Methods and results: The EURO SHOCK trial will test the benefit or otherwise of mechanical cardiac support using VA-ECMO, initiated early after acute percutaneous coronary intervention (PCI) for CGS. The trial sets out to randomise 428 patients with CGS complicating ACS, following primary PCI (P-PCI), to either very early ECMO plus standard pharmacotherapy, or standard pharmacotherapy alone. It will be conducted in 39 European centres. The primary endpoint is 30-day all-cause mortality with key secondary endpoints: 1) 12-month all-cause mortality or admission for heart failure, 2) 12-month all-cause mortality, 3) 12-month admission for heart failure. Cost-effectiveness analysis (including quality of life measures) will be embedded. Mechanistic and hypothesis-generating substudies will be undertaken.

Conclusions: The EURO SHOCK trial will determine whether early initiation of VA-ECMO in patients presenting with ACS-CGS persisting after PCI improves mortality and morbidity.

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SUBMITTED ON 06/09/2020 - REVISION RECEIVED ON 17/10/2020 - ACCEPTED ON 26/10/2020

DOI: 10.4244/EIJ-D-20-01076

Abbreviations

ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ARB	angiotensin receptor blocker
BARC	Bleeding Academic Research Consortium
BCIS	British Cardiovascular Intervention Society
CABG	coronary artery bypass grafting
CGS	cardiogenic shock
CHF	chronic heart failure
CI	confidence interval
CMR	cardiac magnetic resonance
CRT	cardiac resynchronisation therapy
CVD	cardiovascular disease
DSMB	data safety monitoring board
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
EU	European Union
IABP	intra-aortic balloon counterpulsation pump
ICD	implantable cardioverter-defibrillator
ICER	incremental cost-effectiveness ratio
IVRS	interactive voice response system
LV	left ventricle
MACE	major adverse cardiovascular events
MI	myocardial infarction
m-MDT	mini-multidisciplinary team
MSD	mechanical support device
N-STEMI	non-ST-segment elevation myocardial infarction
OHCA	out-of-hospital cardiac arrest
PCI	percutaneous coronary intervention
P-PCI	primary percutaneous coronary intervention
SBP	systolic blood pressure
STEMI	ST-segment elevation myocardial infarction
TSC	trial steering committee
VA-ECMO	veno-arterial extracorporeal membrane oxygenation
VARC	Valve Academic Research Consortium

Introduction

Cardiogenic shock (CGS) occurs in up to 10% of patients with acute coronary syndrome (ACS). It has increased over time, possibly due to better organisation of pre-hospital care, ST-elevation myocardial infarction (STEMI) networks, public education and pre-hospital resuscitation. The US National Inpatient Sample Database reported that the CGS incidence rose from 6.5% to 10.1% from 2003 to 2010[1]. The UK British Cardiovascular Intervention Society (BCIS) audit data showed an increase in primary percutaneous coronary intervention (P-PCI) in the setting of CGS (8.7% in 2015 to 9.1% in 2016)[2].

CGS carries a high mortality (30-day ACS mortality with CGS is reported at 40%-50% **[Supplementary Table 1]** compared to 4% without CGS)[3,4]. Furthermore, 30% of CGS survivors develop chronic heart failure (CHF)[5-7], with its socio-economic implications, high morbidity and poor quality of life, breathlessness, lethargy and debility. Patients carry a burden of ill health requiring admissions for decompensated heart failure, limited return to full-time activities and work, life-long medications and a potential need for expensive therapeutic devices (implantable cardioverter-defibrillator [ICD] and cardiac resynchronisation therapy [CRT])[8].

CGS occurs in >50,000 patients per annum in Europe[9]. The unacceptably high mortality and morbidity, despite contemporary treatments, represents a true unmet clinical need. Once initiated, the pathological process in CGS can be self-perpetuating. A "spiral of decline", difficult to halt once initiated, ultimately leads to death.

Other than culprit artery revascularisation[10], no intervention has shown significant benefit, with marginal benefit from the use of norepinephrine or levosimendan **(Figure 1)**. Most studies on the use of mechanical support devices (MSD), such as veno-arterial extracorporeal membrane oxygenation (VA-ECMO) or heart pumps (e.g., Impella®; Abiomed, Danvers, MA, USA) have been retrospective, and included patients treated in a refractory shock state. Some non-randomised data suggest that early use of MSD may be beneficial[9].

We hypothesise that initiating support prior to adverse compensatory mechanisms will reduce mortality and morbidity. EURO SHOCK will be a robust, prospective, randomised controlled trial to test whether early support with VA-ECMO provides clinical benefit.

Methods

RATIONALE AND DESIGN OF THE EURO SHOCK TRIAL

The EURO SHOCK trial addresses whether early VA-ECMO attenuates the haemodynamic decline, reduces multi-organ failure, and so reduces mortality. It is cited as an ongoing study in the most recent position paper on cardiogenic shock[11].

EURO SHOCK (NCT03813134) is a prospective, randomised, open-label, study design comparing:

Group 1. Immediate PCI + standard care (pharmacological support).

Group 2. Immediate PCI + early peripheral VA-ECMO and standard care (pharmacological support).

The trial flow diagram is shown in **Figure 2**.

The trial hypothesis is that "Early VA-ECMO following revascularisation by PCI in patients with CGS complicating ACS reduces 30-day mortality compared with standard pharmacological support".

The trial is organised into work packages **(Supplementary Table 2)**.

TRIAL CANDIDATES

Patients presenting with ACS (N-STEMI/STEMI) and CGS, including those who have been expeditiously resuscitated, who undergo PCI to the infarct-related artery will be considered for EURO SHOCK, irrespective of PCI success if, after 30 minutes, CGS persists (i.e., insufficient benefit from PCI), provided echocardiography shows no significant mechanical cause (e.g., significant mitral regurgitation).

Trial	Follow-up	n/N	n/N	Mortality Relative risk – 95% CI	Relative risk – 95% CI
Revascularisation (PCI/CABG)					
SHOCK	1 year	81/152	100/150		0.72 (0.54; 0.95)
SMASH	30 days	22/32	18/23		0.87 (0.66; 1.29)
Total		**103/184**	**118/173**		**0.82 (0.69; 0.97)**
Type of revascularisation				Early revascularisation better / Control better	
CULPRIT-SHOCK	30 days	149/184	176/341	Culprit lesion-only PCI better / Immediate multivessel PCI better	0.84 (0.72; 0.98)
Vasopressors					
SOAP-2 (CS subgroup)	28 days	50/145	64/135		0.73 (0.54; 0.97)
Levy et al.	28 days	4/15	5/15		0.80 (0.27; 2.30)
OptimaCC	28 days	8/30	13/27		0.55 (0.27; 1.10)
Total		**62/190**	**82/177**	Norepinephrine better / Dopamine or epinephrine better	**0.70 (0.54; 0.91)**
Inotropes					
Fuhrmann et al.	30 days	5/16	10/16	Levosimendan better / Control better	0.33 (0.11; 0.97)
Glycoprotein IIb/IIIa inhibitors					
PRAGUE-7	In-hospital	15/40	13/40	Upstream abciximab better / Standard treatment better	1.15 (0.59; 2.27)
MO-synthase inhibition					
TRIUMPH	30 days	97/201	76/180		1.14 (0.91; 1.45)
SHOCK II	30 days	24/59	7/20		1.16 (0.59; 2.69)
Cotter et al.	30 days	4/15	10/15		0.40 (0.13; 1.05)
Total		**125/275**	**93/215**	MO-synthase inhibition better / Placebo better	**1.05 (0.85; 1.29)**
Hypothermia					
SHOCK-COOL	30 days	12/20	10/20	Hypothermia better / Control better	1.20 (0.68; 2.17)
IABP					
IABP-SHOCK I	30 days	7/19	6/21		1.28 (0.45; 3.72)
IABP-SHOCK II	30 days	119/301	123/298		0.96 (0.79; 1.17)
Total		**126/319**	**129/319**	IABP better / Control better	**0.98 (0.81; 1.18)**
Mechanical circulatory support					
Thiele et al.	30 days	9/21	9/20		0.95 (0.48; 1.90)
Burkhoff et al.	30 days	9/19	5/14		1.33 (0.57; 3.10)
ISAR-SHOCK	30 days	6/13	6/13		1.00 (0.44; 2.29)
IMPRESS-IN-SEVERE-SHOCK	30 days	11/24	12/24		0.92 (0.50; 1.66)
Total		**35/77**	**32/71**	MCS better / IABP better	**1.01 (0.71; 1.44)**

0 0.25 0.50 0.75 1.0 1.5 2.0 2.5 3.0

Figure 1. *The effect of assessed interventions on outcomes from cardiogenic shock. Modified from Thiele et al*[17].

RATIONALE OF TIMING

Some registry data indicate that the earlier MSD are deployed the better. This has led to the concept that "shock-to-support" times be shortened to the point where some believe that the MSD should be deployed prior to PCI. However, clinicians involved in EURO SHOCK have all seen cases with improvement in haemodynamic parameters following revascularisation of the infarct-related artery, now supported by screening data from the EURO SHOCK trial. To avoid unnecessary, expensive and potentially harmful use of MSD, the EURO SHOCK trial will only randomise after the primary PCI has been completed, but regardless of its success or otherwise.

REASONS FOR TIMING OF MSD IN EURO SHOCK

1. We believe that initiating ECMO, if so randomised, before revascularisation would cause unacceptable delay in PCI, impacting negatively on national audit metrics (e.g., door-to-balloon times).
2. The patient's condition can improve with PCI. Trials that randomise before P-PCI will include a lower-risk group. Those who do not improve after P-PCI (EURO SHOCK) are likely to be higher risk.
3. The time difference between pre-PCI VA-ECMO and post-PCI VA-ECMO will be significantly less than the timing of current clinical scenarios, where ECMO is frequently deployed only as bail-out after several days.

INCLUSION AND EXCLUSION CRITERIA

The trial will consider all patients presenting within 24 hours of ACS with CGS, as defined in the original SHOCK trial[10]. The definition of CGS for the trial will thus be:

"persistent systolic blood pressure (SBP) of <90 mmHg for at least 30 minutes, or the requirement for vasopressor or inotropic therapy to maintain SBP >90 mmHg with clinical signs of pulmonary congestion, plus signs of impaired organ perfusion with at least one of the following manifestations:

– altered mental status
– cold and clammy skin and limbs
– oliguria with a urine output of less than 30 ml per hour

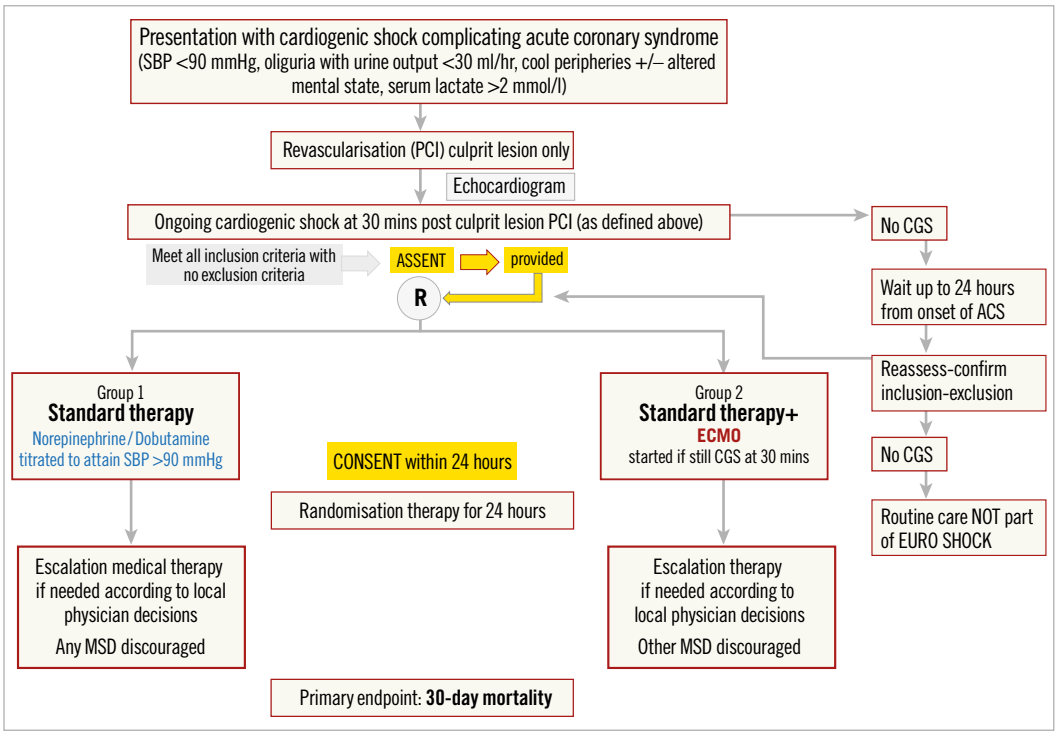

Figure 2. *EURO SHOCK trial flow diagram.*

– elevated arterial lactate level of >2.0 mmol per litre on admission".

Screened patients should fulfil all inclusion with no exclusion criteria **(Supplementary Table 3)**.

THE KEY INCLUSION CRITERIA ARE:

– Willing to provide informed consent/consultee declaration.
– Presentation with a diagnosis of CGS within 24 hours of onset of ACS symptoms.
– CGS secondary to ACS (Type 1 MI STEMI or N-STEMI) or secondary to ACS following previous recent PCI (acute/subacute stent thrombosis, ARC definition).
– Acute PCI has been attempted.
– Persistence of CGS (BP ≤90 mmHg, or need for pharmacological support to maintain BP ≥90 mmHg) assessed 30 minutes after successful or unsuccessful revascularisation of culprit coronary artery.

KEY EXCLUSION CRITERIA:

– Age <18 years and ≥90 years.
– Deemed too frail (Canadian frailty score ≥5).
– Other causes of shock.
– Severe peripheral vascular disease (precluding access and ECMO contraindicated).
– Out-of-hospital cardiac arrest (OHCA) under any of the following circumstances:
  – without return of spontaneous circulation (ongoing resuscitation effort)
  – with pH <7
  – without bystander CPR within 10 minutes of collapse.

OUTCOME MEASURES

PRIMARY ENDPOINT

– The primary endpoint will be all-cause mortality at 30 days.

SECONDARY ENDPOINTS

Key secondary endpoints:

1. All-cause mortality or admission for heart failure at 12 months.
2. All-cause mortality at 12 months.
3. Admission for heart failure at 12 months.

Other secondary endpoints are shown in **Supplementary Appendix 1**.

SAMPLE SIZE AND POWER CALCULATIONS

Data reporting in-hospital/30-day mortality rates in CGS are summarised in **Supplementary Table 1**. The mean 30-day mortality rate is 46.5%.

Mortality varies according to differences in study design and definitions. Some do not include refractory CGS whereas our patients need to remain in CGS post P-PCI and consensus suggests rates of up to 50%[4]. On review of all data and in line with contemporary power calculations from other trials in this arena (DanGer Shock, ECLS-SHOCK), we estimate control group 30-day mortality at 50%. Furthermore, Pöss et al[12] suggest that, based on six variables, there are three risk categories in the IABP-SHOCK II score. Patients in the low-, intermediate-, and high-risk categories have an in-hospital mortality risk of 20-30%, 40-60%, and 70-90%, respectively. We anticipate that patients included in the study will have at least an intermediate score, especially as only patients with persistent CGS 30 minutes post revascularisation will be included.

Some non-randomised studies indicate that VA-ECMO may reduce 30-day mortality by 30-45%[13,14]. A recent meta-analysis suggests a 46% reduction in mortality with VA-ECMO compared with intra-aortic balloon pump (IABP) alone[15]. We judge that a conservative estimate of a 25-30% reduction in 30-day mortality from early VA-ECMO would be regarded as clinically relevant and sufficient for the tested strategy to influence clinicians worldwide should the data support benefit.

Power calculations are based on an anticipated 30-day overall mortality rate of 50% in Group 1 and a 27.5% relative reduction in the primary endpoint in Group 2. To detect this difference with 80% power at a two-sided $\alpha=0.05$, and anticipating a 5% withdrawal rate, 214 patients per group are required (total 428). Power calculations were performed using a log-rank test comparing two survival rates in Stata v14 (StataCorp, College Station, TX, USA).

Two important studies justify our power calculations. The recent categorisation according to the Society for Cardiovascular Angiography and Interventions' (SCAI) definition clearly puts the mortality in groups C (Classic) and D (Doom) at 53.9% and 66.9%, respectively[16]. This is well within the range we have chosen. This is also supported by a recent update, where a figure of approximately 50% is cited[17]. Finally, the numbers of patients adjudged to be required by the ongoing four trials are very similar.

STUDY PROCEDURES

CONSENT

Verbal consent will be obtained from the patient and witnessed by an independent health professional.

Patients may not have the capacity to provide informed consent in the acute CGS setting. If so, then two options will be considered, according to individual country legal agreements.

1. Declaration from a consultee (relative/friend) with specific, separate information documents.
2. Nominated consultee declaration from a physician/health professional, independent and unrelated to the trial (preferably by discussion with relatives). The local principal investigator (PI)/designated person will countersign.

If the patient recovers by 24 hours, then full consent to continue in the study, and retrospective written consent, will be obtained.

If there is no recovery at 24 hours, then consent to continue in the study will again be sought from relatives/physicians.

There are policies in place if the patient or the relatives refuse further consent or if after consent this is subsequently withdrawn.

If consent is withdrawn, only data to that point will be used in the trial.

It should be noted that consent (including verbal consent) has been approved in all countries but with differences to comply with different country laws. The major differences are in Italy where, according to Italian law (d.lgs. 211/2003), the Italian sites will not be asked to enrol unconscious patients.

RANDOMISATION

Assessment of the patient will take place up to 30 minutes after culprit lesion PCI and, irrespective of success, patients will be considered for randomisation providing there is persisting CGS. During this interim time, the ECMO team will be pre-alerted and an echocardiogram undertaken to exclude mechanical causes. A mini-multidisciplinary team (m-MDT) of those involved in patient decision making (including any of physician/interventionist, local EURO-SHOCK PI, ECMO specialist, intensivist) will determine the suitability of the patient for inclusion.

If the patient fulfils all inclusion criteria with no exclusion criteria, following verbal consent, patients will be randomised (1:1), stratified according to presentation following OHCA, to either continuing pharmacological support or immediate peripheral VA-ECMO implantation. Randomisation will be primarily by telephone using a 24/7 interactive voice response system (IVRS), with back-up via the trial-specific web portal.

PATIENT MANAGEMENT

It will be recommended that the patient receives a minimum of 24 hours of their randomised strategy before strategy failure is deemed to have occurred. In patients randomised to standard therapy, MSD use, other than IABP, is discouraged. However, the physician in charge of the patient can allow "up-grading" of therapy (MSD in the standard care arm or additional MSD in the VA-ECMO arm) if, in their opinion, the patient would benefit. Such patients will be included in the intention-to-treat analysis but will be regarded as being in violation of the protocol, and so not included in the per-protocol analysis.

Group 1: standard therapy

Patients allocated to Group 1 will be managed as per standard practice, including inotropic or vasopressor support according to local practice/ESC guidelines[18]. IABP support will be permitted in this group since, based on IABP-SHOCK II, it does not benefit CGS patients[19].

Group 2: immediate VA-ECMO support

In addition to standard care as per Group 1, patients in Group 2 will have peripheral VA-ECMO initiated from 30 minutes after completed P-PCI. VA-ECMO will be deployed as soon as possible and no later than six hours after randomisation, and within 24 hours of CGS diagnosis.

Peripheral VA-ECMO will be as per local practice. All included centres are experienced in VA-ECMO. Methods of left ventricle (LV) unloading, distal limb perfusion, maintenance of ejection/aortic valve opening and anticoagulation will be instituted as per sites' usual care and consistent with VA-ECMO management standards.

Both randomised groups

Accepted and standard contemporary intensive care practices, including mechanical ventilation, will be as required. ECMO weaning in Group 2 will be in accordance with local practice and the patient's clinical status. The aim will be to wean patients from the allocated treatment within seven days. Bridge to further strategies will be in accordance with the patient's clinical condition and the routine practice in that department. In all patients, continuation of post-MI secondary prevention medication will be commenced and according to evidence-based international guidelines.

If a patient recovers from CGS after the PCI but subsequently deteriorates on the intensive care unit (ICU), they can still be considered for the trial but must be randomised within 24 hours of first diagnosis of CGS and be able to receive ECMO, if so randomised, within six hours.

PATIENT FOLLOW-UP

Patients will be followed up after discharge at 30 days (clinic visit), at 6 months (telephone) and at 12 months (clinic visit). Clinical status and admission and post-discharge procedural data will be collected.

STATISTICAL METHODS

The primary analyses will be based on an "intention-to-treat" basis. The primary analysis set will include all patients randomised. A two-sided significance level of 0.05 will be applied. Descriptive statistics for baseline characteristics will be presented by treatment group. The primary endpoint will be compared between groups using a log-rank test, stratified for the presence or absence of OHCA. Patients without an event will be censored at their last follow-up date or 30 days, whichever occurs first. The first two key secondary endpoints will be analysed similarly. For the third key secondary endpoint, mortality will be taken into account as a competing risk. To control the type-1 error, a hierarchical testing strategy will be applied for the key secondary endpoints. Interim analyses for safety are planned, with specific criteria determined by agreement with the data safety monitoring board (DSMB). The trial will not be stopped for futility and there will be no interim analysis for superiority. The DSMB and trial steering committee will monitor the study for feasibility and event rates.

A "per-protocol sub-analysis" will also be undertaken to compare those patients receiving ECMO within six hours and no further MSD (other than IABP to allow LV venting) before hospital discharge (in the intervention group) versus those who did not receive any MSD before hospital discharge (control group).

HEALTH ECONOMIC/COST-EFFECTIVENESS STUDY

We will undertake a robust analysis of costs, outcomes, cost-effectiveness and cost-utility of VA-ECMO compared to the control group. The incremental cost-effectiveness ratio (ICER) will evaluate cost-efficacy. The impact of early VA-ECMO on quality of life and symptoms following recovery from CGS will be measured using the EQ5D (discharge, 30 days, and 6 and 12 months) and Minnesota Living with Heart Failure Questionnaire (discharge and 30 days).

TRIAL SUBSTUDIES (Supplementary Appendix 2)

There are two embedded substudies in EURO SHOCK:

- Cardiac magnetic resonance using novel shortened non-breath-holding protocols to evaluate infarct size, microvascular obstruction, myocardial haemorrhage, LV systolic function, LV volume (n=180).
- Impact of VA-ECMO membrane lining on platelet function (n=100).

ORGANISATION OF THE EURO SHOCK TRIAL

Thirty-nine centres throughout Europe will recruit to EURO SHOCK **(Supplementary Appendix 3)**. Trial committees and sponsor are outlined in **Supplementary Appendix 4**.

TRANSFER SYSTEMS AND EVALUATION OF TIMINGS FOR TRANSFER TO ECMO-CAPABLE CENTRES

Patients in CGS admitted to a non-ECMO centre, who fulfil EURO SHOCK criteria, will be randomised on site. Those randomised to the VA-ECMO arm will immediately be referred to the ECMO centre. Those randomised to the control arm will receive standard treatment at the site of randomisation. Transfer times and delays (between hub and spokes) will be documented. **Figure 3** summarises the transfer of patients based on the type of site that the patient presents to with CGS.

RECRUITMENT TO THE EURO SHOCK TRIAL

Recruitment for the trial commenced in September 2019. The trial was suspended for the COVID pandemic from March 2020 until the end of June 2020, although not all centres reopened at this time. As of October 2020, 10 patients have been recruited (Spain n=3, Norway n=1, Germany n=4, UK n=2).

A total of 55 patients have been screened for the trial. The reasons for exclusion are summarised in **Table 1**.

Table 1. Reasons for screened patients being excluded from the trial.

Main reason patient not included in the trial	N (%)
CGS did not occur within 24 hours of ACS event	7 (13%)
Shock not due to ACS rather secondary to another cause (e.g., sepsis, anaphylaxis, myocarditis)	3 (5%)
PCI was not attempted	3 (5%)
CGS had resolved at 30 mins post PCI	12 (22%)
Mechanical cause for CGS identified (e.g., VSD, ischaemic MR)	9 (16%)
Frailty based on Canadian frailty score	2 (4%)
Dementia	1 (2%)
Severe peripheral vascular disease	2 (4%)
Severe allergy or intolerance	1 (2%)
OHCA: no ROSC/pH <7.0/no bystander CPR within 10 mins of collapse	8 (15%)
Lactate <2.0 mmol/L	1 (2%)
Other	6 (11%)

ACS: acute coronary syndrome; CGS: cardiogenic shock; MR: mitral regurgitation; OHCA: out-of-hospital cardiac arrest; PCI: percutaneous coronary intervention; ROSC: return of spontaneous circulation; VSD: ventricular septal defect

The most common reason for trial exclusion was improvement in the clinical status of patients at 30 minutes post revascularisation, such that they were no longer (by definition) in CGS, emphasising the importance of early revascularisation in avoiding unnecessary use of MSD in this population.

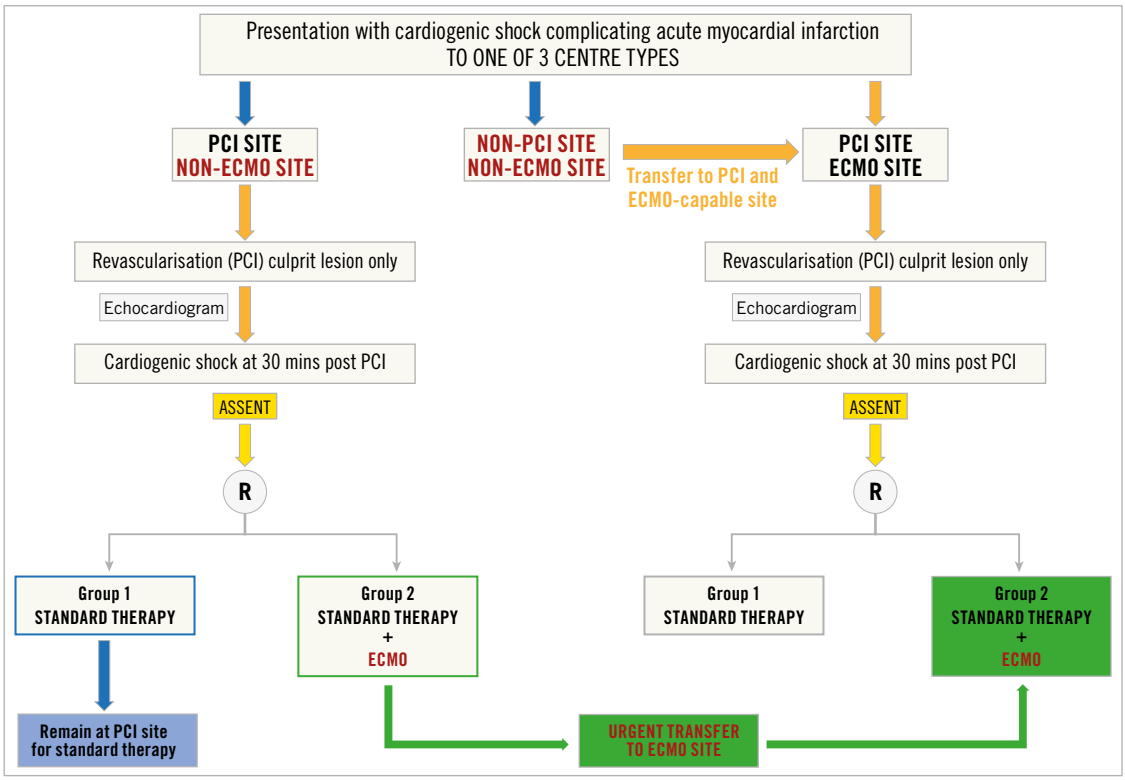

Figure 3. *Patient flow diagram based on type of presenting centre.*

The EURO SHOCK trial has continued to recruit patients while the centres have been open. With an increasing number of sites opening, the projected recruitment rate will increase. We anticipate completion of recruitment within 36 months.

Discussion

In the contemporary era, there has been little decline in mortality beyond that due to revascularisation[10]. A major reason for this is that, despite restoration of myocardial perfusion with PCI, myocardial dysfunction occurs, leading to insufficient cardiac output, with activation of compensatory mechanisms that result in peripheral vasoconstriction, further reduction in peripheral and coronary perfusion, and perpetuation of myocardial ischaemia[20]. Addressing poor cardiac output and maintaining haemodynamic response as optimally and as early as possible could be important in attenuating the "spiral of decline". Mechanical support devices provide haemodynamic support and offer possible solutions. IABP has shown no benefit in CGS[19]. The Impella device has shown limited benefit in small retrospective studies[21,22], possibly due to flow rates with older iterations, or due to timing use. The Impella is currently under evaluation in the DanGer Shock study (NCT01633502).

VA-ECMO allows maintenance of cardiac output to support peripheral organ flow while the heart recovers. However, VA-ECMO is not without potential complications and its cost demands comparative cost-effectiveness analysis. There are conflicting data on the efficacy of VA-ECMO in CGS, with some retrospective studies suggesting a lack of benefit[23,24]. However, a key factor in retrospective studies was the timing of VA-ECMO. Since most were deployed late in the course of CGS, VA-ECMO was less likely to show benefit.

EURO SHOCK is one of five trials currently recruiting comparing the use of MSD with standard therapy in CGS complicating AMI **(Table 2)**. While the inclusion criteria are similar among the trials, when looking specifically at the ECMO trials, a key difference between EURO SHOCK and ECLS-SHOCK is the timing of ECMO implementation. As shown above from the screening data, over 20% of patients who were screened for EURO SHOCK were excluded due to improvement in CGS following PCI – as explained above, the design of EURO SHOCK considers revascularisation first as an important point as this could prevent the use of ECMO with its associated costs and complications in patients who may not require it, while still ensuring that ECMO is commenced early enough to prevent development of refractory shock and multi-organ failure. Both the ANCHOR and ECMO-CS trials include the need for rescue ECMO as part of the primary endpoint, whereas this is a secondary endpoint in EURO SHOCK.

All mechanical support devices have their drawbacks and complications[25-27]. In the case of ECMO, these mostly relate to left ventricular offloading and access-site complications. All centres are ECMO experienced and deal with such issues on a regular basis. We are asking them to perform standard ECMO, which may include the use of IABP for offloading the ventricle. All ECMO complications are listed as serious adverse events (SAE) and will be adjudicated by the independent clinical events committee (CEC) which

Table 2. Current major trials assessing use of MSD in cardiogenic shock complicating acute myocardial infarction.

Study	N	Randomisation groups	Primary outcome
EURO SHOCK (NCT03813134)	428	Patients presenting with CGS complicating acute MI, randomised to either immediate VA-ECMO or standard therapy if persistent CGS 30 mins following revascularisation with PCI. VA-ECMO commenced as soon as possible and no later than 6 hours after randomisation.	Mortality at 30 days.
ECMO-CS (NCT02301819)	120	Patients with rapidly deteriorating or severe cardiogenic shock, randomised to either immediate VA-ECMO or early conservative therapy (including PCI/ cardiac surgery).	Composite: all-cause mortality, resuscitated circulatory arrest and implantation of another MSD at 30 days.
ANCHOR (NCT04184635)	400	Patients presenting with CGS complicating acute MI, randomised to standard therapy including revascularisation, vs standard therapy with VA-ECMO implantation started as soon as possible (commenced in non-ECMO centre by mobile ECMO team prior to patient transfer to ECMO centre).	Treatment failure at 30 days (death in ECMO group, death or rescue ECMO in the control group).
ECLS-SHOCK (NCT03637205)	420	Patients presenting with CGS complicating acute MI, randomised to standard therapy including revascularisation vs standard therapy with VA-ECMO implantation prior to revascularisation.	Mortality at 30 days.
DanGer Shock (NCT01633502)	360	Patients with AMI-CS randomised to standard therapy or Impella CP implanted prior to revascularisation.	Mortality at 180 days.

AMI-CS: acute myocardial infarction - cardiogenic shock; CGS: cardiogenic shock; ECMO: extracorporeal membrane oxygenation; MI: myocardial infarction; PCI: percutaneous coronary intervention; VA-ECMO: veno-arterial extracorporeal membrane oxygenation

will prepare these for the DSMB which can request clarification on ECMO complications through our ECMO advisory board headed by Prof. Alain Vuylsteke. Indeed, one important objective in EURO SHOCK is to determine the clinical risk/benefit as well as the cost/benefit of ECMO used in the strategy tested in this trial.

Limitations

The trial will only evaluate one device, VA-ECMO, and we have been speculative, albeit conservative, in our power calculations, based on the available literature. The trial will be open-label, which could lead to systematic bias; however, independent adjudication and blinding of endpoint evaluation will mitigate the effects of this.

Conclusions

EURO SHOCK is a strategy trial to answer robustly in a sufficiently powered randomised clinical trial whether early intention to treat with VA-ECMO after acute PCI attenuates multi-organ failure, reducing mortality and morbidity in CGS.

The trial is directed by a consortium of experienced clinical academics and will be run to the highest research governance principles.

Impact on daily practice

Should EURO SHOCK demonstrate that VA-ECMO reduces mortality from ACS CGS, it will lead to guideline recommendations, and proposals for the early transfer of CGS patients to ECMO-capable centres within "Shock Networks".

Funding

The EURO SHOCK trial has received funding from the European Union's Horizon 2020 research and innovation programme - grant agreement No. 754946.

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Research Centre, Leicester, United Kingdom. Jeanette Mueller, MSc, PhD; *Accelopment AG, Zurich, Switzerland.* Philip Bousfield, BSc; *Chalice Medical, Worksop, United Kingdom.*

Conflict of interest statement

The following authors disclose grants from the European Union Horizons 2020 programme for the EURO SHOCK study: T. Adriaenssens, C. Berry, K. Bogaerts, A.K. Erglis, G. Guagliumi, S. Haine, A. Kastrati, T. Myrmel, S. Massberg, M. Flather, M. Sabaté, C. Vrints and A. Gershlick. M. Sabate reports personal fees from Abbott Vascular and iVascular. M. Orban reports personal fees from AstraZeneca, Abiomed, Bayer Vital, Cytosorbents, and Sedana Medical, outside the submitted work. C. Berry reports grants and other from Abbott Vascular and AstraZeneca, non-financial support and other from Coroventis, grants and other from GSK, Novartis, other from Neovasc, Medyria, and Siemens Healthcare, and grants and other from HeartFlow, outside the submitted work. G. Guagliumi reports grants and personal fees from Abbott Vascular, personal fees from Boston Scientific, and grants and personal fees from Infraredx, outside the submitted work. P. Bousfield (the managing director of Chalice Medical) is a supplier of equipment used for ECMO in the UK and Europe and as such has commercial interests. Their involvement in the EURO SHOCK trial is such that the use of their equipment is not actively promoted because centres are encouraged to use whatever ECMO devices they are familiar with and use under their current practice. The other authors/study collaborators have no conflicts of interest to declare.

References

1. Kolte D, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, Jain D, Gotsis W, Ahmed A, Frishman WH, Fonarow GC. 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. Ludman PF; on behalf of the British Cardiovascular Intervention Society. BCIS Audit Returns: Adult Interventional Procedures. Jan 2016 to Dec 2016. http://www.bcis.org.uk/wp-content/uploads/2018/03/BCIS-Audit-2016-data-ALL-excluding-TAVI-08-03-2018-for-web.pdf

3. Kunadian V, Qiu W, Ludman P, Redwood S, Curzen N, Stables R, Gunn J, Gershlick A; National Institute for Cardiovascular Outcomes Research. Outcomes in patients with cardiogenic shock following percutaneous coronary intervention in the contemporary era: an analysis from the BCIS database (British Cardiovascular Intervention Society). *JACC Cardiovasc Interv.* 2014;7:1374-85.

4. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline. Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. *Circulation.* 2017;136:e232-68.

5. Shah RU, de Lemos JA, Wang TY, Chen AY, Thomas L, Sutton NR, Fang JC, Scirica BM, Henry TD, Granger CB. Post-Hospital Outcomes of Patients With Acute Myocardial Infarction With Cardiogenic Shock: Findings From the NCDR. *J Am Coll Cardiol.* 2016;67:739-47.

6. Jeger RV, Assmann SF, Yehudai L, Ramanathan K, Farkouh ME, Hochman JS. Causes of death and re-hospitalization in cardiogenic shock. *Acute Card Care.* 2007;9:25-33.

7. Ambrosetti M, Griffo R, Tramarin R, Fattirolli F, Temporelli PL, Faggiano P, De Feo S, Vestri AR, Giallauria F, Greco C. Prevalence and 1-year prognosis of transient heart failure following coronary revascularization. *Intern Emerg Med.* 2014;9:641-7.

8. Kunadian V, Qiu W, Bawamia B, Veerasamy M, Jamieson S, Zaman A. Gender comparisons in cardiogenic shock during ST elevation myocardial infarction treated by primary percutaneous coronary intervention. *Am J Cardiol.* 2013;112:636-41.

9. Thiele H, Ohman EM, Desch S, Eitel I, de Waha S. Management of cardiogenic shock. *Eur Heart J.* 2015;36:1223-30.

10. Hochman JS, Sleeper LA, Webb JG, Sanborn TA, White HD, Talley JD, Buller CE, Jacobs AK, Slater JN, Col J, McKinlay SM, LeJemtel TH. 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.

11. Zeymer U, Bueno H, Granger CB, Hochman J, Huber K, Lettino M, Price S, Schiele F, Tubaro M, Vranckx P, Zahger D, Thiele H. Acute Cardiovascular Care Association position statement for the diagnosis and treatment of patients with acute myocardial infarction complicated by cardiogenic shock: A document of the Acute Cardiovascular Care Association of the European Society of Cardiology. *Eur Heart J Acute Cardiovasc Care.* 2020;9:183-97.

12. Pöss J, Köster J, Fuernau G, Eitel I, de Waha S, Ouarrak T, Lassus J, Harjola VP, Zeymer U, Thiele H, Desch S. Risk Stratification for Patients in Cardiogenic Shock After Acute Myocardial Infarction. *J Am Coll Cardiol.* 2017;69:1913-20.

13. Tsao NW, Shih CM, Yeh JS, Kao YT, Hsieh MH, Ou KL, Chen JW, Shyu KG, Weng ZC, Chang NC, Lin FY, Huang CY. Extracorporeal membrane oxygenation-assisted primary percutaneous coronary intervention may improve survival of patients with acute myocardial infarction complicated by profound cardiogenic shock. *J Crit Care.* 2012;27:530.e1-11.

14. Sheu JJ, Tsai TH, Lee FY, Fang HY, Sun CK, Leu S, Yang CH, Chen SM, Hang CL, Hsieh YK, Chen CJ, Wu CJ, Yip HK. Early extracorporeal membrane oxygenator-assisted primary percutaneous coronary intervention improved 30-day clinical outcomes in patients with ST-segment elevation myocardial infarction complicated with profound cardiogenic shock. *Crit Care Med.* 2010;38:1810-7.

15. Ouweneel DM, Schotborgh JV, Limpens J, Sjauw KD, Engström AE, Lagrand WK, Cherpanath TGV, Driessen AHG, de Mol BAJM, Henriques JPS. Extracorporeal life support during cardiac arrest and cardiogenic shock: a systematic review and meta-analysis. *Intensive Care Med.* 2016;42:1922-34.

16. Schrage B, Dabboura S, Yan I, Hilal R, Neumann JT, Sörensen NA, Goßling A, Becher PM, Grahn H, Wagner T, Seiffert M, Kluge S, Reichenspurner H, Blankenberg S, Westermann D. Application of the SCAI classification in a cohort of patients with cardiogenic shock. *Catheter Cardiovasc Interv.* 2020;96:E213-9.

17. Thiele H, Ohman EM, de Waha-Thiele S, Zeymer U, Desch S. Management of cardiogenic shock complicating myocardial infarction: an update 2019. *Eur Heart J.* 2019;40:2671-83.

18. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 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 J Heart Fail.* 2016;18:891-975.

19. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Böhm M, Ebelt H, Schneider S, Schuler G, Werdan K; IABP-SHOCK II Trial Investigators. Intraaortic balloon support for

myocardial infarction with cardiogenic shock. *N Engl J Med.* 2012;367:1287-96.

20. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. *Circulation.* 2008;117:686-97.

21. O'Neill WW, Schreiber T, Wohns DH, Rihal C, Naidu SS, Civitello AB, Dixon SR, Massaro JM, Maini B, Ohman EM. The current use of Impella 2.5 in acute myocardial infarction complicated by cardiogenic shock: results from the USpella Registry. *J Interv Cardiol.* 2014;27:1-11.

22. Ouweneel DM, Eriksen E, Sjauw KD, van Dongen IM, Hirsch A, Packer EJ, Vis MM, Wykrzykowska JJ, Koch KT, Baan J, de Winter RJ, Piek JJ, Lagrand WK, de Mol BA, Tijssen JG, Henriques JP. Percutaneous Mechanical Circulatory Support Versus Intra-Aortic Balloon Pump in Cardiogenic Shock After Acute Myocardial Infarction. *J Am Coll Cardiol.* 2017;69:278-87.

23. de Waha S, Graf T, Desch S, Fuernau G, Eitel I, Pöss J, Jobs A, Stiermaier T, Ledwoch J, Wiedau A, Lurz P, Schuler G, Thiele H. Outcome of elderly undergoing extracorporeal life support in refractory cardiogenic shock. *Clin Res Cardiol.* 2017;106:379-85.

24. de Waha S, Fuernau G, Desch S, Eitel I, Wiedau A, Lurz P, Schuler G, Thiele H. Long-term prognosis after extracorporeal life support in refractory cardiogenic shock: results from a real-world cohort. *EuroIntervention.* 2016;11:1363-71.

25. Abaunza M, Kabbani LS, Nypaver T, Greenbaum A, Balraj P, Qureshi S, Alqarqaz MA, Shepard AD. Incidence and prognosis of vascular complications after percutaneous placement of left ventricular assist device. *J Vasc Surg.* 2015;62:417-23.

26. Johannsen L, Mahabadi AA, Totzeck M, Krueger A, Jánosi RA, Rassaf T, Al-Rashid F. Access site complications following Impella-supported high-risk percutaneous coronary interventions. *Sci Rep.* 2019;9:17844.

27. Zangrillo A, Landoni G, Biondi-Zoccai G, Greco M, Greco T, Frati G, Patroniti N, Antonelli M, Pesenti A, Pappalardo F. A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. *Crit Care Resusc.* 2013;15:172-8.

Supplementary data

Supplementary Appendix 1. Primary and secondary endpoints of EURO SHOCK.

Supplementary Appendix 2. Substudies.

Supplementary Appendix 3. Lead principal investigators and recruiting centres for the EURO SHOCK study.

Supplementary Appendix 4. Trial committees.

Supplementary Table 1. Review of studies reporting mortality from cardiogenic shock.

Supplementary Table 2. Work package summary.

Supplementary Table 3. Inclusion and exclusion criteria.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-01076

Supplementary data

Supplementary Appendix 1. Primary and secondary endpoints of EURO SHOCK.

Primary endpoint

- All-cause mortality at 30 days

Key secondary endpoints

- All-cause mortality or admission for heart failure at 12 months
- All-cause mortality at 12 months
- Admission for heart failure at 12 months

Other secondary endpoints – during hospital admission

- All-cause mortality
- Cardiovascular (CV) mortality
- Any stroke (categorised as haemorrhagic, ischaemic or unknown)
- Recurrent myocardial infarction (MI)
- Bleeding (BARC type 3-5)
- Escalation to other (non-ECMO) support device for refractory shock
- Any vascular complications (VARC-2 classification)
- Acute kidney injury according to the modified RIFLE classification

Other secondary endpoints – at day 30

- Failure of discharge from primary admission

Other secondary endpoints – at 12 months post discharge

- MACCE (combined endpoint of all-cause mortality, repeat MI, stroke and repeat hospitalisation for heart failure)
- CV mortality
- Recurrent MI
- Any stroke (categorised as ischaemic, haemorrhagic or unknown)
- Need for unplanned (ischaemia-driven) repeat revascularisation (either PCI and/or CABG) after index procedure (planned staged procedures excluded)
- Bleeding (BARC type 3-5)

Cost efficacy outcomes

- Incremental cost-effectiveness ratio (ICER)
- EQ-5D-3L (measured at discharge, six and 12 months)
- Minnesota Living with Heart Failure Questionnaire (measured at discharge)

CMR sub-trial endpoints

- Infarct size
- Microvascular obstruction
- Myocardial haemorrhage
- Left ventricular systolic function
- Left ventricular volume

Supplementary Appendix 2. Substudies

CMR substudy

The purpose of CMR imaging is to assess the nature of myocardial infarct pathology, LV function and remodelling, and correlate these findings with other parameters of outcome, including NT-pro BNP, renal function, and NYHA heart failure grade. Information from control Group 1 will be particularly relevant. We will also investigate mechanistic differences between the treatment groups (infarct size, microvascular obstruction, myocardial haemorrhage, LV systolic function, LV volume, renal size, perfusion, etc.). Multiparametric cardiovascular MRI, including renal imaging where feasible, will be performed following randomisation in up to 30 days as soon as clinically feasible (when feasible) and repeated at six months. Participation in the CMR substudy will be confirmed through a feasibility questionnaire. We anticipate that the substudy may be feasible in about ~40% of early survivors in the trial population (allowing for centre feasibility, patient compliance, etc.), thus the sample size in this substudy is 180. For a minimum between-group difference in peak circumferential strain of 0.05 and a standard deviation of 0.10, a two-sided t-test at a significance level (alpha) of 0.05, then 63 and 84 subjects with data in each group would be needed to reject the null hypothesis of no difference with 80% and 90% power (1-beta), respectively.

Platelet substudy

Our industry partner Chalice Medical Ltd (UK) have incorporated a CE mark proprietary coating for its oxygenator. We will test further its impact on platelet activation in a simple small substudy run by Prof. Stan Heptinstall from "Platelet Solutions Ltd". Since not all clinical sites use Chalice ECMO and as we wish centres to use what they are currently using, we will compare platelet function in 100 patients (50 who have been supported with an ECMO circuit incorporating the Chalice oxygenator and 50 with an oxygenator from any other manufacturer). The patients will not be randomised. The samples will be analysed at "Platelet Solutions Ltd UK". Small (5 ml) blood samples will be taken from the patients at up to five time points before, during and after the clinical procedure for analysis of platelet function. They will be collected using a one tenth volume (0.5 ml) of 3.8% (w/v) trisodium citrate dihydrate as anticoagulant. Each sample will be analysed using a kit supplied by Platelet Solutions Ltd (Nottingham, UK) to investigate the level of platelet activation before (baseline) and after activation with three platelet stimulants, followed by fixation. The fixed and stabilised samples are then posted to a central flow cytometry facility for analysis of platelet surface-located P-selectin, thus enabling quantitation of the level of platelet activation achieved. The overall analytical procedure will provide valuable information on changes in platelet function consequent to the clinical procedure.

Supplementary Appendix 3. Lead principal investigators and recruiting centres for the EURO SHOCK study.
(lead/country PIs in bold)

Centres involved in EURO SHOCK	**Lead investigator**
England	
0101 UHL	Banning/Yusuff
0103 Papworth Hospital	Hoole
0104 Barts Heart Centre London	Jain
0105 Kings College Hospital	Patel
0106 Harefield Brompton London	Rosenberg
0107 Guys	Barrett
0109 Derby	Chitkara
0110 Kettering	Raju
0111 Lincoln	Lee
Germany	
0201 Deutsches Herzzentrum München	**Kastrati**
0202 Klinikum rechts der Isar	Ibrahim/Laugwitz
0203 Universitäts-Herzzentrum Freiburg-Bad Krozingen	Valina
0801 Medizinische Universität Wien	Hengstenberg/Distelmaier
0207 Ludwig-Maximilians-Universität München	**Massberg/Orban**
0208 Klinikum Campus Innenstadt	Brunner
0210 Uniklinikum Tübingen	Schlensak
Scotland	
University of Glasgow	**Berry**
0108 Golden Jubilee National Hospital	Berry

Belgium	
0301 Katholieke Universiteit Leuven	**Adriaenssens**
0302 Algemeen Stedelijk Ziekenhuis Aalst	Buysschaert
0303 Onze Lieve Vrouw Hospital Aalst	De Raedt
0304 Jessa Ziekenhuis Hasselt	Timmermans
0305 Imelda Bonheiden	Dewilde
0306 University Hospital Antwerpen	**Haine/Vrints**
0307 ZNA Middelheim	Vermeersch
0308 AZ Gent	De Pauw
0309 AZ Monica	Everaert
0310 AZ Sint-Jan (Brugge)	Dewulf
0311 UCL (Bruxelles)	Van Caenegem
0401 Consorci Institut D'Investicacions Biomediques August Pi i Sunyer/Hospital Clinic de Barcelona	**Sabaté**
0402 Hospital de Bellvitge	Ariza-Sole
0403 Hospital Germans Trias i Pujol	Mauri
0404 Hospital Vall d'Hebron	Garcia del Bianco
0405 Hospital de Sant Pau	Serra/Sionis
Norway	
0501 Universitetssykehuset Nord Norge	**Myrmel**
Latvia	
0601 Paula Stradina Liniska Universitates Slimnica AS	**Erglis**
Italy	

0701 Azienda Ospedaliera Papa Giovanni XXIII	**Guagliumi**
0702 Azienda Universitaria Ospedaliera Careggi, Florence	Di Mario
0703 Ospedale San Giovanni Bosco di Torino	Bocuzzi
0704 University Hospital of Bologna Policlinico S. Orsola – Malpighi	Saia

Supplementary Appendix 4. Trial committees

Trial Chief Investigator: Professor A.H. Gershlick*
Sponsor: University of Leicester

Trial Committees

- **Steering Committee**

Chair: Prof. Anthony Gershlick*; Independent Chair: Prof. Frans Van de Werf

- **Independent DSMB:**

Chair: Prof. Freek Verheugt
Members: Dr Kadir Caliskan, Prof. Jan Tijssen

- **Clinical Events Committee:**

Chair: Dr Fernando Alfonso
Members: Dr Rob Byrne, Dr Marco Valgimigli, Dr Elizabeth J. Haxby

Trial co-ordination

The trial central co-ordinating centre is the University of Leicester. The EURO SHOCK trial is a pan-European consortium of research centres, with the study being divided into nine interlinked work packages **(Supplementary Table 2)**.

The trial organisation consists of a trial steering committee (Chairs: Prof. A. H. Gershlick*, Prof. F. Van de Werf), a clinical events committee (Chair: Dr F. Alfonso) and an independent data safety & monitoring board (DSMB) (Chair: Prof. F. Verheugt).

The Trial Steering Committee (TSC) will be responsible for scientific conduct of the study, ensure clinical governance, and provide guidance for issues arising during the study to recruiting centres. They will also co-ordinate a publication policy.

The Data Safety and Monitoring Board (DSMB) will monitor the safety and ethical conduct of the study and outcomes and, with the support of an independent statistician, feed back to the TSC on a regular basis.

The Clinical Events Committee (CEC) will independently adjudicate all clinical events.
In addition to the standard committees, EURO SHOCK also has the following advisory boards:

- External Advisory Board & Ethics Committee (Chair: Dr Art Slutsky)
- ECMO Advisory Panel (Chair: Dr A. Vuylsteke)

The External Advisory Board will provide advice on scientific and technological matters as well as patient-related issues and will work with the DSMB regarding review of ethical conduct of the study. The ECMO advisory panel is composed of experts in the field of ECMO and will develop a standard guidance for the deployment of ECMO technology as well as providing technical expertise to the TSC pertaining to any issues around use of ECMO in the trial.

Clinical Trials Unit

University of Glasgow
Lead: Dr Sharon Keane
Assistant: Claire Kerr

*We regret to announce the death of Professor Gershlick.

Supplementary Table 1. **Review of studies reporting mortality from cardiogenic shock.**

Paper	Nature of cardiogenic shock patients included	Mortality rates reported
Strom et al. EuroIntervention. 2018;13:e2152-9.	US adults admitted with CGS from 2004 to 2014, comparing those receiving MCS and no MCS (n=183,516).	In-hospital mortality No MCS=41.5% With MCS=32.7%
Overtchouk et al. EuroIntervention. 2018;13:e2160-8.	Observational single-centre study from the ACTION study group recruiting 106 consecutive patients, with CS secondary to MI to ECLS pre or post PCI with or without IABP. Revascularisation successful in 76% of patients, half of the patients had severe triple-vessel coronary artery disease.	30-day mortality rate=63.2%.
Kolte et al. J Am Heart Assoc. 2014;3:e000590.	2003–2010 US Nationwide Inpatient Sample databases to identify all patients ≥40 years of age with STEMI and cardiogenic shock. Compared outcomes with and without early mechanical revascularisation and/or IABP.	In-hospital mortality No early mechanical revascularisation/IABP=44.6% Early mechanical revascularisation/IABP=33.8%
Goldberg et al. Circ Cardiovasc Qual Outcomes. 2016;9:117-25.	5,686 patients analysed between 2001 and 2011 who developed cardiogenic shock while in hospital following initial admission without features of cardiogenic shock but acute MI.	In-hospital case fatality rate=41.4%.
Goldberg RJ et al. Circulation. 2009;119:1211-9.	13,663 patients hospitalised with AMI between 1975 and 2005, with 6.6% of patients developing cardiogenic shock.	In-hospital mortality=65.4%. Case fatality rate lower from 2001 onwards (42.1% in 2001, 48.9% in 2003, 42.0% in 2005).
Babaev et al. JAMA. 2005;294:448-54.	Prospective, observational study of 293,633 patients with ST-elevation myocardial infarction (25,311 [8.6%] had cardiogenic shock; 7,356 [29%] had cardiogenic shock at hospital presentation) enrolled in the National Registry of Myocardial Infarction (NRMI) from January 1995 to May 2004 at 775 US hospitals with revascularisation capability.	In-hospital cardiogenic shock mortality decreased from 60.3% in 1995 to 47.9% in 2004.
Holmes et al. Circulation. 1999;100:2067-73.	Patients enrolled from GUSTO-IIb trial admitted with STEMI/NSTEMI; n=12,804 with 4.2% of STEMI and 2.5% of NSTEMI patients developing cardiogenic shock.	In-hospital mortality in cardiogenic shock patients: STEMI patients=63% NSTEMI patients=73%
Jensen JK et al. Int J Cardiol Heart Vasc. 2015;6:19-24.	Study including all patients admitted with STEMI from 2002 to 2010 in a single centre, comparing mortality with and without cardiogenic shock and also with and without use of IABP.	30-day cumulative mortality in cardiogenic shock=57.3%
McNeice A et al. Catheter Cardiovasc Interv. 2018;92:E356-E367.	A retrospective study of 649 patients from the British Columbia Cardiac Registry with cardiogenic shock, AMI and MVD. Specifically looking at impact of culprit vs complete revascularisation in cardiogenic shock patients.	30-day mortality=34.5% in MVPCI, 23.7% in culprit PCI only. 1-year mortality=44.3% in MVPCI, 32.6% in culprit PCI only.

Xie A et al. J Cardiothorac Vasc Anaesth. 2015;29:637-45.	Meta-analysis of patients with cardiogenic shock or cardiac arrest undergoing ECMO. Data here are based on meta-analysis subgroup analysis of patients receiving ECMO treatment for cardiogenic shock alone.	30-day mortality=47.5%.
Thiele et al. N Engl J Med. 2012;367:1287-96.	IABP-SHOCK II trial. 300 patients presenting with CS randomised to IABP or no-IABP.	30-day mortality=41.3% in non-IABP group.
Thiele et al. N Engl J Med. 2017;377:2419-32.	CULPRIT-SHOCK.	30-day all-cause mortality: Multivessel PCI group=51.6% Culprit-only PCI group=43.3%
Shah M et al. Circ Heart Fail. 2018;11:e004310.	43,212 patients with AMI and cardiogenic shock from the 2013 to 2014 Healthcare Cost and Utilization Project National Readmission Database.	In-hospital mortality=39.8%. (30-day readmission for CCF=20.6%).
Anderson ML et al. Circ Cardiovasc Qual Outcomes. 2013;6:708-15.	Analysis of patients presenting with NSTEMI and STEMI to 392 US hospitals between 2007 and 2011 (approx. 24,000 patients with cardiogenic shock).	STEMI patients in-hospital mortality=33.1% NSTEMI patients in-hospital mortality=40.8%
Wayangankar S et al. JACC Cardiovasc Interv. 2016;9:341-51.	Review of trends in management and outcomes of patients with cardiogenic shock from the NCDR CathPCI registry. The patients were analysed according to 4 time blocks: 2005 to 2006, 2007 to 2008, 2009 to 2010, and post–2010 (2011 to 2013).	Unadjusted in-hospital mortality: 2005–2006: 27.6% 2007–2008: 27.4% 2009–2010: 28.2% 2011–2013: 30.6%
Patel SM et al. ASAIO J. 2019;65:21-8.	Retrospective analysis of patients with refractory cardiogenic shock treated with either VA ECMO +/- surgical venting (n=36) or VA ECMO + Impella (n=36).	30-day mortality rates: VA-ECMO=78% VA-ECMO+Impella=57%
Isorni MA, Danchin N et al. Arch Cardiovasc Dis. 2018;111:555-63.	Retrospective analysis of incidence, management and 1-year mortality in patients from the FAST-MI registry (1995–2010).	1-year mortality in 2010 Male: 48% Female: 54%
Aissaoui et al. Eur J Heart Fail. 2016;18:1144-52.	Retrospective analysis of elderly patients (defined as age ≥75 yrs) presenting with MI and cardiogenic shock from the FAST MI registry.	1-year mortality in 2010=59%.
Lee JM et al. J Am Coll Cardiol. 2018;71:844-56.	Retrospective analysis from the KAMIR-NIH registry.	1-year mortality: Multivessel PCI=21.3% IRA-only PCI=31.7%

Kunadian et al. JACC Cardiovasc Interv. 2014;7:1374-85.	Retrospective analysis of data from the BCIS NICOR registry of patients with cardiogenic shock.	30-day mortality=37.3%.
Chung et al. Int J Cardiol. 2016;223:412-17.	65 patients with profound cardiogenic shock post-MI requiring ECMO support.	In-hospital mortality=53.8%
Sheu et al. Crit Care Med. 2010;38:1810-7.	335 patients, including those with profound and non-profound cardiogenic shock and those with and without ECMO.	Overall 30-day mortality without ECMO=60.9% 30-day death without ECMO or profound CS=33.3% 30-day death without ECMO but profound CS=72%
Ouweneel et al. J Am Coll Cardiol. 2017;69:278-87.	IMPRESS study.	30-day mortality: IABP group=50%, Impella group=46%.

Supplementary Table 2. Work package summary.

The work is funded by the European Union Horizons 2020 research and innovation programme under grant agreement No. 754946. The applicants were a consortium of 13 partners with work separated into nine work packages (WP):

WP1: Data Management. Lead: Dr S. Keane, Prof. I. Ford (Glasgow CTU)
WP2: Trial Set-Up. Lead: Prof. A. Gershlick (University Leicester)
WP3: Clinical Trial Programme. Lead: Prof. A. Gershlick (University Leicester)
WP4: Clinical Follow-Up, Data Monitoring and Safety Evaluation. Lead: Prof. S. Haine, Prof. C. Vrints (University Antwerpen)
WP5: Statistical Analysis. Lead: Dr K. Bogaerts (Katholieke Universiteit Leuven)
WP6: Health Economic Cost Efficacy Analysis. Lead: Prof. M. Flather and Prof. R. Fordham (University East Anglia)
WP7: CMR Sub-Study. Lead: Prof. C. Berry (University of Glasgow)
WP8: Public Engagement, Dissemination and Exploitation. Lead: Prof. T. Adriaenssens (Katholieke Universiteit Leuven)
WP9: Coordination and Management. Lead: Prof. A. Gershlick (University Leicester)
Trial PI: Prof. A. Gershlick
Co-chairs Trial Steering Committee: Prof. A. Gershlick, Prof. F. Van de Werf
DSMB chair: Prof. F. Verheugt
Clinical Events Committee Chair: Dr F. Alfonso

Supplementary Table 3. Inclusion and exclusion criteria.

Inclusion criteria
All of the following are required for inclusion: 1. Willing to provide informed consent/consultee declaration. 2. Presentation with a diagnosis of CGS within 24 hrs of onset of ACS symptoms 3. CGS secondary to ACS (Type 1 MI STEMI or N-STEMI) or secondary to ACS following previous recent PCI (acute/subacute stent thrombosis ARC definition). 4. PCI has been attempted 5. Persistence of CGS 30 minutes after successful or unsuccessful revascularisation of culprit coronary artery CGS will be defined by: • Systolic blood pressure <90 mmHg for at least 30 minutes, or a requirement for a continuous infusion of vasopressor or inotropic therapy to maintain systolic blood pressure >90 mmHg. • Clinical signs of pulmonary congestion, plus signs of impaired organ perfusion with at least one of the following manifestations: • altered mental status • cold and clammy skin and limbs • oliguria with a urine output of less than 30 ml per hour • elevated arterial lactate level of >2.0 mmol per litre on admission. 6. Provision of verbal consent followed by patient consent (or consultee declaration if the patient is unable to provide consent) 7. Age >=18 yrs and <90 yrs.
Exclusion criteria
1. Unwilling to provide informed consent/consultee declaration 2. Echocardiographic evidence (recorded within 30 minutes of end of PCI procedure) of mechanical cause for CGS: e.g., ventricular septal defect, LV-free wall rupture, ischaemic mitral regurgitation 3. Age <18 yrs and >=90 years 4. Deemed too frail (Canadian frailty score >5) 5. Shock from another cause (sepsis, haemorrhagic/hypovolaemic shock, anaphylaxis, myocarditis, etc.) 6. Significant systemic illness 7. Known dementia of any severity 8. Comorbidity with life expectancy <12 months 9. Severe peripheral vascular disease (precluding access making ECMO contraindicated) 10. Severe allergy or intolerance to pharmacological or antithrombotic antiplatelet agents 11. Out-of-hospital cardiac arrest (OHCA) under **any** of the following circumstances: ➢ without return of spontaneous circulation (ongoing resuscitation effort) ➢ with pH <7 ➢ without bystander CPR within 10 minutes of collapse 12. Involved in another randomised research trial within the last 12 months 13. Pregnant or nursing mother