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Venoarterial extracorporeal membrane oxygenation or standard care in patients with cardiogenic shock complicating acute myocardial infarction: the multicentre, randomised EURO SHOCK trial

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KEYWORDS

- ACS/NSTE-ACS
- cardiogenic shock
- STEMI

Abstract

Background: Cardiogenic shock (CGS) occurs in 10% of patients presenting with acute myocardial infarction (MI), with in-hospital mortality rates of 40-50% despite revascularisation.

Aims: The EURO SHOCK trial aimed to determine if early use of venoarterial extracorporeal membrane oxygenation (VA-ECMO) could improve outcomes in patients with persistent CGS following primary percutaneous coronary intervention (PPCI).

Methods: This multicentre, pan-European trial randomised patients with persistent CGS 30 minutes after PPCI of the culprit lesion to receive either VA-ECMO or continue with standard therapy. The primary outcome measure was 30-day all-cause mortality in an intention-to-treat analysis. Secondary endpoints included 12-month all-cause mortality and 12-month composite of all-cause mortality or rehospitalisation due to heart failure.

Results: Due to the impact of the COVID-19 pandemic, the trial was stopped before completion of recruitment, after randomisation of 35 patients (standard therapy n=18, VA-ECMO n=17). Thirty-day all-cause mortality occurred in 43.8% of patients randomised to VA-ECMO and in 61.1% of patients randomised to standard therapy (hazard ratio [HR] 0.56, 95% confidence interval [CI]: 0.21-1.45; p=0.22). One-year all-cause mortality was 51.8% in the VA-ECMO group and 81.5% in the standard therapy arm (HR 0.52, 95% CI: 0.21-1.26; p=0.14). Vascular and bleeding complications occurred more often in the VA-ECMO arm (21.4% vs 0% and 35.7% vs 5.6%, respectively).

Conclusions: Due to the limited number of patients recruited to the trial, no definite conclusions could be drawn from the available data. Our study demonstrates the feasibility of randomising patients with CGS complicating acute MI but also illustrates the challenges. We hope these data will inspire and inform the design of future large-scale trials.

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Abbreviations

ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ARNI	angiotension receptor/neprilysin inhibitor
AT2	angiotensin II receptor type 2
BARC	Bleeding Academic Research Consortium
CABG	coronary artery bypass graft
CFS	clinical frailty score
CGS	cardiogenic shock
CPR	cardiopulmonary resuscitation
eGFR	estimated glomerular filtration rate
IABP	intra-aortic balloon pump
LV	left ventricle
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
OHCA	out-of-hospital cardiac arrest
PCI	percutaneous coronary intervention
PPCI	primary percutaneous coronary intervention
ROSC	return of spontaneous circulation
SAE	serious adverse events
VA-ECMO	venoarterial extracorporeal membrane oxygenation

Introduction

Cardiogenic shock (CGS) remains an important cause of morbidity and mortality as a complication of acute myocardial infarction (MI). It occurs in approximately 10% of cases following MI[1,2]. Although the seminal SHOCK trial demonstrated significant improvement in mortality following revascularisation in such patients[3], the rates of 30-day mortality remain at about 50% with no change over the past decade in retrospective analyses[2] or randomised trials[4,5].

Mechanical circulatory support (MCS) devices provide haemodynamic support in patients presenting with CGS. This immediate and temporary support may preserve organ perfusion in patients presenting with CGS, thus allowing time for revascularisation and reperfusion to enable sufficient recovery of cardiac function for restoration of haemodynamic stability.

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a short-term mechanical circulatory support device that offers additional oxygen delivery when the cardiac output is insufficient to supply cellular demands due to left and/or right ventricle failure. This offers physiological flow rates that can potentially support both the left and right ventricle. Although some historical studies suggest minimal benefit of this, most of these used VA-ECMO in refractory CGS, when the spiral of decline caused by the shock state may have become irreversible.

The EURO SHOCK trial aimed to assess whether early use of VA-ECMO in patients with CGS complicating acute MI and persisting post-primary percutaneous coronary intervention (PCI) could result in reductions in 30-day and 12-month mortality.

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Methods

The study rationale, design and sample size calculation have been reported previously[6]. The trial was conducted in accordance with the Declaration of Helsinki and approved by the ethics committees of participating centres. The CONSORT checklist is provided in **Supplementary Appendix 1**. ClinicalTrials.gov: NCT03813134.

TRIAL PARTICIPANTS

A total of 15 centres from 6 countries participated in the trial. A list of the centres and the number of patients screened and recruited at each centre are provided in **Supplementary Table 1**.

Patients presenting with CGS due to myocardial infarction and who had had attempted/successful primary PCI (PPCI) of the culprit lesion were enrolled if there was persistent CGS 30 mins after the procedure. The definition of CGS and the inclusion criteria have been published previously[6]. In essence, it is defined by the presence of systolic blood pressure (SBP) <90 mmHg or maintained above 90 mmHg with the addition of vasopressor or inotropic support, with evidence of hypoperfusion. All patients had a bedside echocardiogram within 30 mins post-PCI to exclude the presence of a structural complication as the cause of CGS (e.g., ventricular septal rupture, ischaemic mitral regurgitation, left ventricular free-wall rupture). The inclusion and exclusion criteria are outlined in **Supplementary Table 2**.

TRIAL PROCEDURES

Patients were randomised to receive VA-ECMO as soon as possible − within 6 hours of randomisation − or continue standard therapy in a 1:1 fashion. Intra-aortic balloon pump (IABP) use was permitted as a means of left ventricular unloading in patients receiving VA-ECMO therapy. Randomisation was carried out using a web-based randomisation system stratified by out-of-hospital cardiac arrest (OHCA). Where possible, informed consent was obtained from the patients. If the patients were not able to provide informed consent, then a process of initial consent was employed followed by confirmation of informed consent by the patient if they regained consciousness or the capacity to provide consent. If confirmation of consent was not possible, the patients remained in the study. The trial flow diagram is shown in **Supplementary Figure 1**.

The use of mechanical support devices in the control therapy group was discouraged, although the use of IABP was still permitted in this group. However, if physicians felt this was in a patient's interest to manage clinical deterioration, it was permitted but acknowledged as a protocol violation. In the VA-ECMO group, IABP was the only permitted means of left ventricular (LV) unloading.

TRIAL ENDPOINTS

The primary endpoint was 30-day all-cause mortality. Secondary endpoints included in-hospital major bleeding complications

(BARC type 3-5); cerebrovascular events; vascular complications, as defined by the Valve Academic Research Consortium-2 (VARC-2) criteria[7]; 12-month all-cause mortality; and the composite endpoint of 12-month mortality and readmission with heart failure. Quality-of-life outcomes at 30 days were assessed using the EQ-5D-3L questionnaire and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

All endpoint-related events were independently adjudicated by the clinical events committee **(Supplementary Appendix 2)**.

SAMPLE SIZE

The study aimed to recruit 428 patients to demonstrate a 27.5% reduction in the primary endpoint with 80% power and α=0.05. This was based on an anticipated 30-day mortality of 50% in the standard therapy group. Details of the sample size calculation have been published previously[6].

STATISTICAL ANALYSIS

The primary analysis was performed according to the intention-to-treat principle. A prespecified secondary as-treated analysis was also performed according to whether the patients received early VA-ECMO or not.

Categorical variables are expressed as percentages and compared using Pearson's chi-squared or Fisher's exact tests where applicable. Continuous variables are expressed as mean±standard deviation or median with interquartile range (IQR) and compared using a t-test or Mann-Whitney U test, respectively.

The time to occurrence of the primary endpoint was analysed using the Kaplan-Meier method and compared using a log-rank test. The hazard ratio (HR) with a 95% confidence interval (CI) was obtained from a Cox proportional hazards model stratified for OHCA. Event rates of secondary endpoints, not including mortality, were determined from cumulative incidence functions, taking mortality as a competing risk into account. The comparison between groups was performed using Gray's test, stratified by OHCA and using mortality as a competing risk. An HR with a 95% CI was obtained from a Fine and Gray model with the baseline hazard stratified by OHCA and taking mortality as a competing risk.

The analysis was performed using SAS/STAT software, Version 9.4 of the SAS System for Windows (SAS Institute).

Results

TRIAL FLOWCHART

An overview of screening and recruitment to the trial is shown in **Figure 1**.

From January 2020 to January 2022, a total of 333 patients were screened at the recruiting centres. Of them, 35 patients (13.25%) were recruited to the trial **(Supplementary Table 1)**: 18 patients were randomised to standard therapy and 17 patients to early VA-ECMO.

The main reasons for screening failure included out-of-hospital cardiac arrest without return of spontaneous circulation (ROSC) or bystander cardiopulmonary resuscitation (CPR) within 10 minutes (20% of patients), recovery from CGS after PCI (18%), CGS secondary to another cardiac cause and not associated with acute MI (14%) **(Figure 1)**.

Among the patients randomised to the VA-ECMO group, 5 patients did not receive VA-ECMO therapy (complications with vascular access or difficulty with peripheral cannulation leading to abandoning the implantation of VA-ECMO n=3; patient refusal n=1; withdrawal of consent n=1). In the standard therapy arm, there was no crossover to VA-ECMO within the predefined time frame of 6 hours. However, 1 patient from this group received VA-ECMO after this 6-hour period due to clinical deterioration. This patient has been included in the standard therapy arm for the "intention-to-treat" and the "as-treated" analyses. Hence, for the as-treated population, 22 patients received standard therapy and 12 patients received VA-ECMO. Results of the as-treated set are presented in **Supplementary Figure 2** and **Supplementary Figure 3**.

BASELINE CHARACTERISTICS

The baseline characteristics of the recruited patients are outlined in **Table 1**. These were similar between the 2 treatment groups.

The median age was 67 years (range: 38-83 yrs) in the standard therapy group and 68 years (range: 45-76 yrs) in the VA-ECMO group.

The extent of myocardial infarction and left ventricular dysfunction was similar between the 2 groups. The peak troponin values were also similar between the 2 groups: median peak troponin standard therapy: 1,780 ng/L (IQR 321-125,000); median peak troponin VA-ECMO group: 1,608 ng/L (IQR 536-7,490). The admission and peak lactate levels were numerically higher in the standard therapy group, although the subsequent peak lactate levels during the intensive therapy unit admission and pH levels were similar between groups. The degree of shock in both groups was similar as reflected by comparable scores with the Simplified Acute Physiology Score (SAPS II), Acute Physiology and Chronic Health Evaluation II (APACHE II), sequential organ failure assessment (SOFA) and vasoactive-inotropic score (VIS) **(Table 1)**.

The estimated left ventricular ejection fraction (LVEF) on admission was also comparable between the 2 groups and classed as severely impaired in both groups (standard therapy median LVEF: 25% [IQR 15-35%]; VA-ECMO median LVEF: 20% [IQR 10-35%]).

Both groups had comparable times from the onset of CGS to the initial angiogram (median time 3 hours [IQR 2-5 hrs] in the standard therapy group and median time 2 hours [IQR 1-4 hrs] in the VA-ECMO group), as well as the times from the onset of CGS to primary PCI (median time 4 hrs [IQR 2-6 hrs] vs 2 hrs [IQR 1-4 hrs], respectively) **(Supplementary Table 3)**. Angiographic and procedural characteristics and the success of primary PCI was also well matched between the 2 groups.

The median time from CGS onset to VA-ECMO was 4.8 hours (IQR 3.7-6.5 hrs). The median time from first medical contact

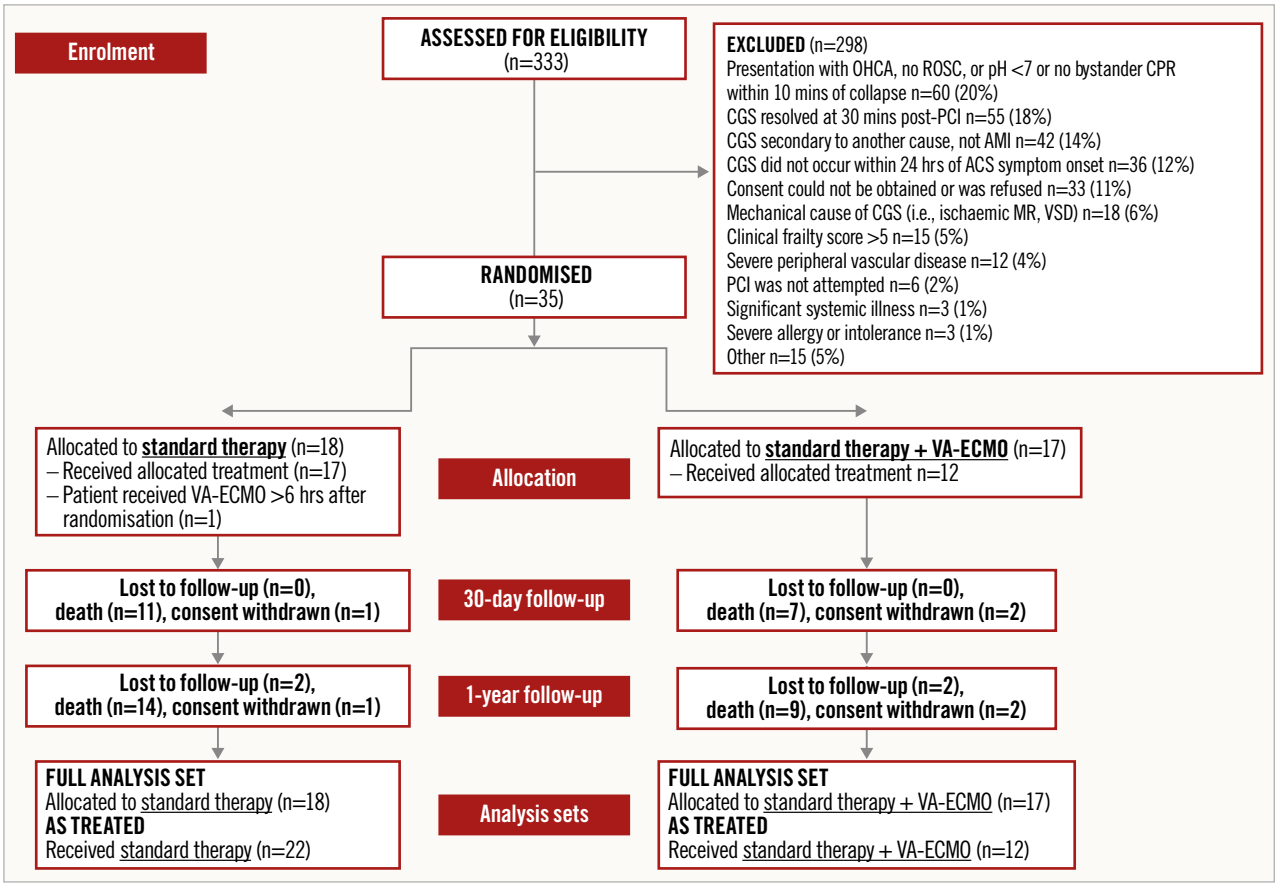

Figure 1. *Consort diagram for the EURO SHOCK trial recruitment. ACS: acute coronary syndrome; AMI: acute myocardial infarction; CGS: cardiogenic shock; CPR: cardiopulmonary resuscitation; MR: mitral regurgitation; OHCA: out-of-hospital cardiac arrest; PCI: percutaneous coronary intervention; ROSC: return of spontaneous circulation; VA-ECMO: venoarterial extracorporeal membrane oxygenation; VSD: ventricular septal defect*

(FMC) to VA-ECMO insertion was 4.4 hours (IQR 4.2-8.8 hrs). The timings from presentation to randomisation and implementation of the randomised strategy are summarised in **Supplementary Table 3**.

PRIMARY OUTCOME MEASURE: 30-DAY ALL-CAUSE MORTALITY

The primary outcome of 30-day all-cause mortality occurred in 43.8% (7/17) of patients randomised to the VA-ECMO group and in 61.1% (11/18) of patients randomised to standard therapy (HR 0.56, 95% CI: 0.21-1.45; p=0.22) **(Figure 2)**.

The primary outcome was also numerically lower in the as-treated analysis (HR 0.40, 95% CI: 0.13-1.26; p=0.105) **(Supplementary Figure 2)**.

SECONDARY OUTCOME MEASURES

The secondary in-hospital outcomes are described in **Table 2**.

There were numerically lower rates of all-cause and cardiovascular death, ischaemic stroke, recurrent MI and acute kidney injury in patients randomised to VA-ECMO. In contrast, and as expected given the additional procedural nature of VA-ECMO, a numerically higher number of vascular complications and major bleeding events were observed in patients randomised to the VA-ECMO group. In terms of non-cardiovascular death, the predominant cause of death in both groups was from hypoxic brain injury **(Supplementary Table 4)**.

There was a noticeably higher rate of failure of discharge from primary admission at 30 days with those patients randomised to standard therapy (83.3% compared with 57.1% in the VA-ECMO group). Left ventricular function assessment at 30 days is summarised in **Supplementary Appendix 3**.

QUALITY-OF-LIFE OUTCOMES AT 30 DAYS POST-DISCHARGE

There were a limited number of EQ-5D-3L questionnaires completed at 30 days in both the standard therapy (n=2) and VA-ECMO (n=4) groups. The responses are summarised in **Supplementary Table 5**. Among the EQ-5D-3L respondents, in the standard therapy group, there were no reported problems with mobility, self-care, or usual activities at 30 days, while half of the respondents from the VA-ECMO group reported some difficulties in these domains at 30 days. Similar responses for anxiety/depression were reported at 30 days in both groups.

Similarly, there were limited responses from the Minnesota Living with Heart failure Questionnaire (2 responses at 30-day

Table 1. Baseline characteristics.

Baseline characteristic	Standard therapy (n=18)	VA-ECMO (n=17)
Gender		
Male	16/18	13/16
Female	2/18	3/16
Age, yrs	65±12	66±9
	67 (56-77)	68 (60-73)
	38-83	45-76
Race		
Southeast Asian	1/18	0/15
Caucasian	17/18	15/15
Smoking status		
Current	6/17	4/14
Former	7/17	4/14
Never	4/17	6/14
Hypertension	10/14	10/15
Diabetes	5/16	7/14
Type I	0/5	0/7
Type II	5/5	7/7
Diabetes treatment		
Oral agents	2/5	4/7
Insulin and oral agents	1/5	2/7
Diet only	1/5	0/7
Unknown	1/5	1/7
Family history of ischaemic heart disease	1/8	0/4
Renal disease	4/16	1/13
Dialysis	0/4	0/1
CKD stage		
Stage 2A	1/4	0/1
Stage 3A	3/4	1/1
Prior cerebrovascular event	1/16	0/15
Non-TIA	1/1	-
Prior MI	3/15	1/15
STEMI	1/3	0/1
NSTEMI	2/3	1/1
Prior PCI or CABG	6/16	2/15
Prior PCI	5/6	2/2
Prior CABG	1/6	0/2
Prior admission for heart failure	0/16	0/16
Dyslipidaemia	7/8	4/6
Peripheral arterial disease	2/9	0/7
Preadmission medications		
Aspirin	4/5	2/4
Anticoagulant	1/5	0/4
Statins	3/5	3/4
ACE inhibitor	1/5	1/4

Table 1. Baseline characteristics (cont'd).

Baseline characteristic	Standard therapy (n=18)	VA-ECMO (n=17)
AT2 blocker	1/5	1/4
Beta blocker	2/5	2/4
Diuretic	3/5	0/4
ARNI	1/5	0/4
Other	2/5	1/4
Lab results		
Peak troponin, ng/L	1,780 (321-125,000)	1,608 (536-7,490)
Haemoglobin, g/L	138±23	117±41
White cell count, x10^9/L	18±6	18±8
Platelet, x10^9/L	250±4	233±88
Urea, mmol/L	8±5	6±2
Creatinine, mg/dL	1.5±0.5	1.2±0.4
eGFR, mL/min/1.73 m^2	51±16	53±22
Admission lactate, mmol/L	8.2±4.6	5.9±3.7
Peak lactate, mmol/L	10.2±3.7	8.1±4.8
pH	7.22 (7.07-7.34)	7.18 (7.12-7.26)
CRP, mg/L	20±48	28±43
NT-proBNP, ng/L	4,133±7,799	5,442±8,726
BMI, kg/m^2	28±4	27±5
Blood pressure - admission		
Systolic BP, mmHg	107±38	90±23
	95 (81-125)	82 (75-105)
Diastolic BP, mmHg	68±27	55±15
	58 (52-80)	55 (46-60)
Intubated	12/16	8/12
Highest VIS score	75 (18-312)	67 (5-102)
Highest SAPS II 0-48 hr	52 (47-67)	61 (51-83)
Highest APACHE II 0-48 hr	21 (19-28)	32 (9-37)
Highest SOFA 0-48 hr	10 (7-12)	9 (4-12)
Killip class		
Class II	0/17	1/13
Class III	1/17	0/13
Class IV	16/17	12/13
Neurological assessment		
Conscious and alert with good cerebral performance	5/12	4/9
Conscious with moderate cerebral impairment	2/12	0/9
Comatose	5/12	5/9
Glasgow Coma Scale	9±6	8±6
	8 (3-15)	3 (3-15)
	3-15	3-15
Location of MI		
Anterior	7/16	3/14
Inferior	2/16	5/14

Table 1. Baseline characteristics (cont'd).

Baseline characteristic	Standard therapy (n=18)	VA-ECMO (n=17)
Lateral	0/16	3/14
Anterolateral	6/16	3/14
Inferolateral	1/16	0/14
Echocardiographic data		
Echo performed (post-randomisation)	12/17	11/13
LVEF, %	30±24	23±12
	25 (15-35)	20 (10-35)
Mitral regurgitation	5/12	0/11
LV thrombus	0/12	0/11
Angiographic data		
Single vessel disease	12/18	8/14
Multivessel disease	6/18	6/14
Diseased vessels (DS >50%)		
1VD	5/18	7/16
2VD	1/18	3/16
3VD	5/18	3/16
LMS isolated	4/18	0/16
LMS + 1VD	0/18	1/16
LMS + 2VD	1/18	1/16
LMS + 3VD	6/18	1/16
IRA lesion location		
Prox RCA	4/18	2/16
Mid RCA	0/18	3/16
Acute marginal	1/18	0/16
LMS	4/18	2/16
Prox LAD	7/18	5/16
Mid LAD	1/18	2/16
Prox LCx	1/18	1/16
Mid LCx	0/18	1/16
Previous CABG	1/18	0/16
Attempted PCI	16/18	14/16
Stent implanted	15/18	15/16
DES	15/15	15/15
TIMI flow pre-PCI		
TIMI 0	11/18	10/16
TIMI 1	3/18	1/16
TIMI 2	1/18	3/16
TIMI 3	3/18	2/16
TIMI flow post-PCI		
TIMI 0	0/18	3/16
TIMI 1	1/18	0/16
TIMI 2	2/18	1/16
TIMI 3	15/18	12/16
IABP inserted	8/18	3/16
Pre-PCI	2/8	1/3
Post-PCI	5/8	2/3
Post-randomisation	1/8	0/3
Any NIRA lesions	11/18	7/16
Total number NIRA lesions	39	23
PCI to NIRA lesions	4/39	1/23
Anticoagulant regimen		
Heparin	18/18	16/16
Bivalirudin	0/18	0/16
Antiplatelet regimen		
Aspirin	16/18	14/16
Clopidogrel	8/18	3/16
Prasugrel	6/18	7/16
Ticagrelor	4/18	5/16
Cangrelor	1/18	2/16
GP IIb/IIIa inhibitor	3/18	0/16
Out-of-hospital cardiac arrest		
No. of patients	8/18	9/17
Time to ROSC, min	19±18	27±20
	13 (8-31)	16 (15-50)
	5-46	15-50
Cardiac arrest rhythm		
PEA	1/6	0/3
VF	5/6	3/3

Data are expressed as n/N, mean±standard deviation, median (IQR) or range.
ACE: angiotensin-converting enzyme; AT2: angiotensin II receptor type 2; ARNI: angiotensin receptor/neprilysin inhibitor; BMI: body mass index; BP: blood pressure; CABG: coronary artery bypass graft; CKD: chronic kidney disease; CRP: C-reactive protein; DES: drug-eluting stent; DS: diameter stenosis; eGFR: estimated glomerular filtration rate; IABP: intra-aortic balloon pump; IQR: interquartile range; IRA: infarct-related artery; LAD: left anterior descending; LCx: left circumflex; LMS: left main stem; LV: left ventricle; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NIRA: non-infarct-related artery; NSTEMI: non-ST-segment elevation myocardial infarction; NT-proBNP: N-terminal pro-brain natriuretic peptide; PCI: percutaneous coronary intervention; PEA: pulseless electrical activity; RCA: right coronary artery; ROSC: return of spontaneous circulation; SD: standard deviation; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischaemic attack; TIMI: Thrombolysis in Myocardial Infarction; VD: vessel disease; VF: ventricular fibrillation

clinic in the standard therapy group and 3 responses in the VA-ECMO group). Lower scores were reported for both the physical (standard therapy median: 38 [IQR 28-47]; VA-ECMO median: 13 [IQR 8-34]) and emotional (standard therapy median: 20 [IQR 10-30]; VA-ECMO median: 6 [IQR 5-13]) components of the questionnaire. The total median scores were 86 (IQR 58-114) in the standard therapy group and 33 (IQR 21-73) in the VA-ECMO group.

IN-HOSPITAL SERIOUS ADVERSE EVENTS

There was a total of 11 patients with a serious adverse event (SAE) during admission (31.43%: 5 in the standard therapy group and 6 in the VA-ECMO group). The reported SAEs are summarised in

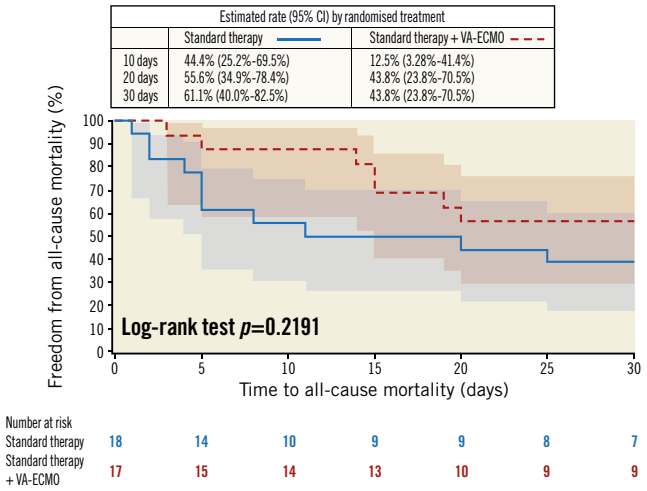

Figure 2. *Primary endpoint of 30-day all-cause mortality – intention-to-treat analysis. CI: confidence interval; VA-ECMO: venoarterial extracorporeal membrane oxygenation*

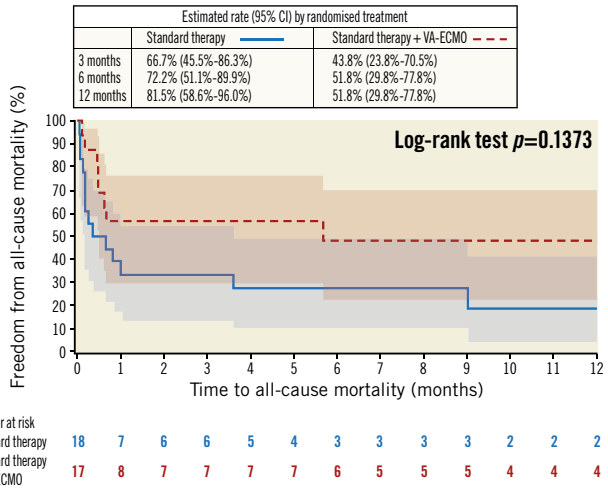

Figure 3. *12-month all-cause mortality – intention-to-treat analysis. CI: confidence interval; VA-ECMO: venoarterial extracorporeal membrane oxygenation*

Table 2. In-hospital outcomes – intention-to-treat analysis.

	Standard therapy	VA-ECMO + standard therapy
Total number of patients	18	17
All-cause death	13/18 (72)	7/14 (50)
CV death	6/18 (33)	2/14 (14)
Stroke	2/18 (11)	0/14 (0)
Ischaemic stroke	2/18 (11)	0/14 (0)
Recurrent myocardial infarction	2/18 (11)	0/14 (0)
Major bleeding (BARC 3-5)	1/18 (6)	5/14 (36)
Escalation to other (non-VA-ECMO) support device for refractory shock	1/6 (17)	0/5 (0)
Escalation to VA-ECMO (crossover)	1/18 (6)	NA
Any vascular complications	0/18 (0)	3/14 (21)
Acute kidney injury	8/18 (44)	4/14 (29)
Failure of discharge from primary admission	15/18 (83)	8/14 (57)

Data are N or n/N (%). Percentages are Kaplan-Meier or cumulative incidence estimates. BARC: Bleeding Academic Research Consortium; CV: cardiovascular; VA-ECMO: venoarterial extracorporeal membrane oxygenation

Supplementary Table 6, with similar types and numbers demonstrated between the randomised groups.

ONE-YEAR OUTCOME DATA

All-cause mortality at 12 months was numerically lower in the VA-ECMO group; this occurred in 51.8% (8/17) of patients randomised to the VA-ECMO group and in 81.5% (14/18) patients randomised to standard therapy (HR 0.52, 95% CI: 0.21-1.26; p=0.14) **(Figure 3)**.

Twelve-month all-cause mortality was also numerically lower in the as-treated analysis **(Supplementary Figure 3)**.

The 12-month composite endpoint of all-cause mortality and readmission with heart failure was also numerically lower in the VA-ECMO group: VA-ECMO group: 59.8% (9/17); standard therapy group: 79.2% (14/18) (HR 0.57, 95% CI: 0.24-1.34; p=0.19).

The rates of 12-month readmission for heart failure were similar between the treatment arms: VA-ECMO group: 8.0% (1/17); standard therapy group: 6.9% (1/18) (HR 1.19, 95% CI: 0.11-13.22; p=0.89). LVEF assessed at 12 months is summarised in **Supplementary Appendix 3**.

Discussion

The results of this study show that in patients with persistent CGS secondary to acute MI 30 mins after attempted or successful revascularisation of the culprit lesion, early implementation of VA-ECMO resulted in numerically lower rates of 30-day and 1-year mortality. The overall recruitment to the trial was significantly impacted by the COVID-19 pandemic, and less than 10% of the initially planned recruitment was completed. As a result, no definitive conclusions can be drawn from these data. However, the results do indicate a trend to a benefit from early use of VA-ECMO in this setting, supporting further clinical trials in this area. The potential benefit would have to be compared with the higher potential complications associated with the use of VA-ECMO in this setting, as shown in the results of this study. Thus, any future studies in this area would have to demonstrate any benefit from VA-ECMO outweighing the potential risks and complications associated with the use of this highly invasive mechanical circulatory support device.

During the recruitment period, only 13% of the screened patients were considered eligible for inclusion to the trial. As outlined in **Figure 1**, the most common reasons for screening failures were out-of-hospital cardiac arrest without ROSC or bystander CPR within 10 minutes (20%) and recovery from CGS after PCI (18%). With regard to the out-of-hospital cardiac arrest patients,

the study aimed to include patients who would be most likely to receive the greatest benefit from use of VA-ECMO. Patients who received continuous CPR with no ROSC (which would effectively constitute ECMO-CPR rather than the use of VA-ECMO in CGS) or patients who had a prolonged period following cardiac arrest without CPR were considered to have a worse prognosis and lower chances of neurological recovery and were thus excluded from the trial, as the use of VA-ECMO is unlikely to be of benefit. Similarly, recovery of CGS following PPCI was also excluded, as, in such patients, VA-ECMO is unlikely to confer additional benefit. It is likely that use of an MCS device in patients with CGS complicating acute MI may be beneficial to a distinct cohort of CGS patients whose outcome from the shock state can be improved by the use of VA-ECMO or another MCS device, and, where any additional treatment is not likely to be futile. The timing of the use of VA-ECMO, either before or after the PCI attempt, remains an area of interest and uncertainty. Although patients can improve with PCI alone, as shown in the recruitment data of this trial, there are retrospective data potentially indicating a benefit from early haemodynamic support and stabilisation prior to PCI with an MCS device. Such a strategy of upfront VA-ECMO would need to confirm a benefit beyond any potential risks of using VA-ECMO, and this remains an active area of research with forthcoming trials, such as in the ECLS-SHOCK trial (Clinical.Trials.gov: NCT03637205)[8]. Determining which patients are most likely to benefit from VA-ECMO or other MCS devices is another aspect of further research in this area, possibly through *post hoc* analyses of larger trials. Such information could be of benefit in future trials.

This study allowed physicians to undertake standard therapy as per their usual practice in the management of patients with CGS following PPCI. Although there are some data to indicate how such patients can be managed, these patients can be a heterogenous population in terms of shock state post-PPCI and their response to therapy. Thus, a pragmatic design was used allowing physicians to tailor treatment according to response with standard therapy while assessing the additional benefit of VA-ECMO in the intervention arm of the trial. This strategy also accounted for heterogeneity in clinical practice that can occur across intensive care units in Europe recruiting patients to a trial.

In addition, the trial only permitted LV unloading with an IABP. There are several methods of unloading the LV while the patient is on a VA-ECMO, including potentially using an Impella (Abiomed) or atrial septostomy. However, to date, there are no compelling data to support one modality over the other or to indicate in which patients or when to unload the LV[9]. The trial was not pragmatically designed to investigate any additional benefit of LV unloading in the context of peripheral VA-ECMO nor to determine the optimal modality of LV unloading. The use of an Impella for LV unloading was discouraged, as this may have confounded any effect of VA-ECMO in the intervention arm of the trial, especially as Impella may also have a role in the management of cardiogenic shock[10]; this is being evaluated in the setting of CGS complicating acute MI in the DanGer Trial (ClinicalTrials.gov: NCT01633502)[11].

Although we attempted to ensure no crossover therapy between the standard and VA-ECMO groups, there were 5 patients who were randomised to VA-ECMO but did not receive the study intervention. This was mainly due to difficulties in peripheral cannulation (3/5), with 2 of the 5 cases due to patient refusal or withdrawal of consent. Anticipating this potential for patients not being able to receive the allocated treatment, an "as-treated" analysis was also undertaken which, again mindful of the low numbers of participants, continues to demonstrate a potential, if non-significant, benefit for VA-ECMO in those patients that received this treatment. Again, this would need to be confirmed in larger-scale randomised controlled trials; however, the principle of a prospective "as-treated" analysis would be important to mitigate the impact of potential crossovers in such trials.

In contrast to other studies that have suggested no benefit of VA-ECMO use in refractory CGS[12,13], the patients randomised to VA-ECMO within this trial received ECMO at a median of 4.8 hrs from the time of onset of CGS. This is commensurate with timings of other studies that suggested a benefit from VA-ECMO in this setting[14,15]. Thus, the potential benefit derived from VA-ECMO or other mechanical support devices is likely driven by early haemodynamic support before maladaptive physiological responses have occurred because of the low cardiac output state, which inevitably leads to multiple organ failure and consequent mortality.

The EURO SHOCK trial only included patients who had persistent CGS 30 mins after revascularisation. While some have suggested that upfront use of a mechanical support device before revascularisation may lead to a greater derived benefit from these devices, as alluded to from a subset of data from the USpella Registry[10], there is a potential risk of including patients who would otherwise recover from PCI without further intervention, potentially exposing such patients to high risk complications associated with invasive devices. Indeed, from the screening logs of this trial, 18% of patients who were not recruited had early resolution of CGS following revascularisation.

The recently reported ECMO-CS trial showed no difference in the primary composite endpoint of death from any cause, resuscitated circulatory arrest and implementation of another circulatory support device at 30 days between those patients who received immediate VA-ECMO and those who did not (63.8% in the immediate VA-ECMO group, 71.2% in the non-early VA-ECMO group; HR 0.72, 95% CI: 0.46-1.12; p=0.21). Similarly, no difference was seen in the individual components of the primary endpoint nor adverse secondary outcomes[16].

Although the ECMO-CS study seems at odds with the indication of early improvement seen in outcomes with VA-ECMO from this study, it should be noted that 39% of patients enrolled to the non-early VA-ECMO arm of ECMO-CS did receive VA-ECMO or another mechanical support device due to a deterioration in their clinical condition. The mean time to VA-ECMO insertion in these crossover patients was 1.9 days. This crossover effect has

been cited in other trials involving the use of ECMO, such as the EOLIA trial[17], as being a possible reason for diluting any potential benefits of ECMO use and a reason why this was discouraged in the standard therapy group in EURO SHOCK. In addition, ECMO-CS did not exclusively include patients with CGS secondary to acute myocardial infarction – only 74 patients of the 117 analysed patients that were recruited had CGS secondary to acute MI. Therefore, recovery and subsequent weaning would be dependent on recovery from the underlying cause of shock, whereas in acute MI patients, VA-ECMO use is envisaged to support organ perfusion in the time following PCI where revascularised myocardium can recover.

The finding of a numerically lower rate of 30-day mortality in the VA-ECMO group in EURO SHOCK is commensurate with similar reported benefits in other studies. Sheu et al showed a significantly lower 30-day mortality in patients who received VA-ECMO in the catheterisation lab following confirmation of refractory shock, despite IABP use, compared with IABP alone[14].

A small pilot study randomising patients with CGS to immediate VA-ECMO or standard therapy showed a numerically lower rate of 12-month mortality in the VA-ECMO group[18]. However, as with the EURO SHOCK trial, this study recruited 42 patients, therefore, the number of patients was too low to draw meaningful conclusions. In addition, 12-month mortality was a secondary outcome measure in this study; the primary outcome was improvement in LV function at 30 days, as measured by echocardiography, and the study showed no benefit of VA-ECMO in this respect[19]. Also, it is noteworthy that at 30 days, only 1 patient had died in the control group, implying that this study had recruited lower-risk CGS patients.

Thirty-day all-cause mortality in the EURO SHOCK control group was 61.1%, suggesting that the population recruited to the trial were not "lower-risk" CGS patients. This is consistent with data on 30-day mortality reported from other retrospective analyses[2]. It is likely that we were able to exclude patients who would recover with revascularisation alone by allowing an appropriate window of time following PPCI and before randomisation[20].

The findings of this study do indicate potential benefit from early use of VA-ECMO in CGS patients. There are currently 2 other large scale randomised controlled trials, ECLS-SHOCK and the ANCHOR trial (ClinicalTrials.gov: NCT04184635) comparing mostly upfront use of VA-ECMO prior to revascularisation and VA-ECMO compared with standard therapy, respectively. These trials should provide further insight into the use of VA-ECMO in CGS patients.

In evaluating the impact of the use of VA-ECMO in survival from CGS, it is important to ascertain whether survival is associated with a good quality of life. Although we attempted to assess quality-of-life outcomes at 30 days with both the EQ-5D-3L and Minnesota Living with Heart Failure Questionnaire (MLHFQ), there were low response rates for both questionnaires at follow-up. The low number of responses is a result of the overall number of patients recruited to the trial and the consequent number of patients surviving in each group at 30 days, as well as the expected response rate from such questionnaires. Given the high 30-day mortality associated with CGS, it is imperative to ensure a high a rate of completion of questionnaires in both the control and intervention arms at follow-up to ensure data that can inform whether any potential mortality benefit also translates into sustained or improved quality of life. Strategies that could be employed to obtain optimal response rates could include ensuring completion of questionnaires at the time of follow-up in the clinics and limiting the number of questionnaires that patients are asked to complete. Due to the small numbers of completed questionnaires, it is difficult to draw any meaningful conclusions on the impact on quality of life for patients surviving CGS and having had VA-ECMO.

Limitations

The key limitation of this trial is the low recruitment, due mainly to the COVID-19 pandemic. Trial recruitment was stopped early, predominantly because of the impact of the COVID-19 pandemic. Trial recruitment was suspended at different time periods during the trial in participating centres due to the need to utilise ECMO resources for COVID-19 patients. Consequentially, the reported results are significantly underpowered to draw meaningful conclusions on the utility of VA-ECMO in this setting.

Although there were no prespecified weaning criteria for patients placed on VA-ECMO, we decided to allow intensive care physicians to undertake weaning as they felt appropriate according to the clinical condition of the patient; this allowed for a more pragmatic reflection on how patients presenting in such circumstances are treated if placed on VA-ECMO and how they should be evaluated in the trial. All centres involved in the trial were experienced ECMO centres.

Conclusions

Due to the limited number of patients recruited to the trial, no definite conclusions could be drawn from the available data on the use of VA-ECMO in CGS complicating acute myocardial infarction. There could be a potential role for VA-ECMO in CGS; however, the efficacy and safety of VA-ECMO in this setting would need to be assessed in larger RCTs. These data may contribute to future meta-analyses of forthcoming RCTs comparing the use of VA-ECMO with standard care in CGS patients following acute myocardial infarction.

Impact on daily practice

Although underpowered because of poor recruitment, the findings from the trial support further randomised clinical trials into the early use of VA-ECMO in cardiogenic shock complicating acute myocardial infarction that does not improve following primary PCI of the culprit lesion.

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Conflict of interest statement

M. Orban reports receiving payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Abbott Medical, AstraZeneca, Abiomed, Bayer Vital, Biotronik, Bristol-Myers Squibb, CytoSorbents, Daiichi Sankyo Deutschland, Edwards Lifesciences, and Sedana Medical. T. López-Sobrino reports receiving payments or honoraria for presentations from the University of Barcelona and the European Acute Cardiac Care Association. T. Adriaenssens reports receiving honoraria from Abiomed for speakers' bureaus. C. Berry is employed by the University of Glasgow, which holds research agreements for his work with Abbott Vascular, AstraZeneca, Boehringer Ingelheim, and HeartFlow; and holds consultancy and research agreements for his work with Abbott Vascular, AstraZeneca, Auxilius Pharma, Boehringer Ingelheim, Causeway Therapeutics, Coroventis, Genetech, GSK, HeartFlow, Menarini, Neovasc, Siemens Healthcare, and Valo Health. D. Adlam has received funding to support a clinical research fellow from Abbott Vascular; funding from AstraZeneca for unrelated research; has conducted unrelated consultancy for GE HealthCare; holds patents for medical devices, including a cardiac assist device (EP3277337A1, PCT/GB2017/050877, UK PATENT APPLICATION NUMBER 2211616.4); and has received royalties from Elsevier Inc. for ECG made Practical and ECG Problems books. M. Flather reports

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Supplementary data

Supplementary Appendix 1. CONSORT checklist.

Supplementary Appendix 2. Trial Committees & Clinical Trials Unit

Supplementary Appendix 3. Left ventricular function.

Supplementary Table 1. Screening and recruitment data according to recruiting site.

Supplementary Table 2. Inclusion and exclusion criteria for EURO SHOCK.

Supplementary Table 3. In-hospital serious adverse events.

Supplementary Table 4. Timing of intervention and VA-ECMO implantation in study cohort.

Supplementary Table 5. Quality of life at 30-day clinic using the EQ-5D-3L questionnaire.

Supplementary Table 6. Causes of in-hospital non-cardiovascular death.

Supplementary Figure 1. Trial flow diagram for EURO SHOCK.

Supplementary Figure 2. Primary outcome of 30-day all-cause mortality in the "as-treated" population.

Supplementary Figure 3. Secondary outcome of 12-month all-cause mortality in the "as-treated" population.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-23-00204

Supplementary data

Supplementary Appendix 1. CONSORT checklist.

Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORTreporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	3
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	6
Background and objectives	#2b	Specific objectives or hypothesis	7
Methods			
Trial design	#3a	Description of trial design (such as parallel,	7

		factorial) including allocation ratio.	
Trial design	#3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	n/a
Participants	#4a	Eligibility criteria for participants	7
Participants	#4b	Settings and locations where the data were collected	8
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	9
Sample size	#7a	How sample size was determined.	9
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomization - Sequence generation	#8a	Method used to generate the random allocation sequence.	
n/a (in primary outcome publication)			
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size)	
n/a (in primary outcome publication)			
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	n/a (in primary outcome publication)
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned	n/a (in primary outcome

		participants to interventions	publication)
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how.	n/a
Blinding	#11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	9
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	10
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	10
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	10
Recruitment	#14b	Why the trial ended or was stopped	10
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	10
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10
Outcomes and	#17b	For binary outcomes, presentation of both absolute	10

estimation		and relative effect sizes is recommended	
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	11
Harms	#19	All important harms or unintended effects in each group (For specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	13
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
Registration	#23	Registration number and name of trial registry	2
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	13
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
Registration	#23	Registration number and name of trial registry	2
Protocol	#24	Where the full trial protocol can be accessed, if available	n/a
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	1

Notes:

- 8a: n/a (in primary outcome publication)
- 8b: n/a (in primary outcome publication)
- 9: n/a (in primary outcome publication)

- 10: n/a (in primary outcome publication) The CONSORT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 16. April 2023 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

Supplementary Appendix 2. Trial Committees & Clinical Trials Unit

Trial Committees

Trial Steering Committee:

Chairs: Dr David Adlam, Prof Frans Van Der Werf (Independent Chair)

Data Safety and Monitoring Committee:

Chair: Prof. Freek W.A. Verheugt

Members: Prof Jan Tijssen, Dr. Kadir Caliskan and Dr. Alain Vuylsteke.

Clinical Events Committee:

Members: Dr Alain Vuylsteke, Prof Pascal Vrancx

CEC co-ordinator: Dr Amerjeet Banning

Clinical Trials Unit

Robertson Centre for Biostatistics, University of Glasgow.

CTU team: Sharon Keane, Claire Kerr, Mairi Warren, Sarah Boyle.

Supplementary Appendix 3. Left ventricular function.

Follow-up echocardiographic data were available for a total of 7 patients at 30 days (n=3 for V-A ECMO and n=4 for standard therapy). The mean LVEF was 47% +/- 14% in the V-A ECMO group, compared with 37% +/- 17% in the standard therapy group.

At 12-month follow-up, echocardiographic data were available for 5 patients (n=4 in V-A ECMO group and n=1 for standard therapy group). The mean LVEF was 47% +/- 14% in the V-A ECMO group, compared with 31% in the standard therapy group.

Supplementary Table 1. Screening and recruitment data according to recruiting site.

Centre	Local PI/research nurse	Number of patients screened	Number of patients recruited
Spain			
Hospital Clinic de Barcelona	Prof Manel Sabate/Dr Teresa Lopez-Sobrino	81	8
Hospital Germans Trias I pujol	Dr Victoria Vilalta/Dr Fina Mauri	16	2
Hospital Vall d'Hebron	Dr Irene Buera	33	3
Hospital de Sant Pau	Dr Alessandro Sionis/ Antonia Serra	3	1
Hospital de Bellvitge	Dr Albert Ariza	5	0
Germany			
Deutsches Herzzentrum Muenchen	Prof Adnan Kastrati/Prof Steffen Massberg/Monika Neumeyer	54	2
Ludwig Maximillian Universitaet	Dr Martin Orban/Monika Baylacher	18	11
Klinkium Campus Innenstadt	Prof Stefan Brunner	7	1
UK			
Glenfield Hospital, Leicester	Dr Hakeem Yusuff/Dr Amerjeet Banning	14	1
King's College Hospital, London	Dr Sameer Patel/Sheetale Patale	22	2
Harefield and Royal Brompton	Dr Alex Rosenberg	7	0
Norway			
Universitetssykehuset Nord-Norge	Prof Truls Myrmel/Felix Bohm	32	3
Latvia			
Pauls Stradins Kliniska Universitates Slimnica AS	Prof Andrejs Erglis/Dr Aija Maca-Kaleja	39	1
Belgium			
KU Leuven	Dr Tom Adriaenssens	1	0
University Hospital Antwerpen	Dr Steven Haine	1	0

Supplementary Table 2. Inclusion and exclusion criteria for EURO SHOCK.

Inclusion Criteria
Willing to provide informed consent / consultee declaration
Presentation with Cardiogenic Shock within 24hrs of onset of ACS symptoms
CGS secondary to Type I MI (STEMI or NSTEMI), or secondary to ACS following recent PCI (Acute/Subacute stent thrombosis)
PCI has been attempted
Persistent of CGS for 30 mins after successful or unsuccessful attempt at revascularisation of culprit artery
Age >18yrs and <90 yrs.
Exclusion Criteria
Unwilling to provide informed consent / consultee declaration
Echo evidence of mechanical complication causing CGS (VSD, Ischaemic MR, LV free-wall rupture)
Age <18 yrs or >90 yrs
Deemed too frail (CFS>5)
Shock from another cause (sepsis, hypovolaemic, anaphylaxis, haemorrhagic)
Significant systemic illness
Known dementia of any severity
Comorbidity with life expectancy <12 months
Severe PVD (precluding access for VA-ECMO)
Severe allergy or intolerance to pharmacological or antithrombotic antiplatelet agents.
OHCA under any of the following circumstances: • Without ROSC (ongoing CPR) • With pH<7 • Without bystander CPR within 10 mins of collapse
Involved in another randomised research trial within the last 12 months
Pregnant or nursing mother

ACS = acute coronary syndrome; CFS = Clinical Frailty Score. CPR = Cardiopulmonary Resuscitation; LV=left ventricular; MR= mitral regurgitation, MI=myocardial infarction, OHCA = out-of-hospital cardiac arrest; PVD = Peripheral Vascular Disease. ROSC = Return of Spontaneous Circulation. VSD= ventricular septal defect.

Supplementary Table 3. Timing of intervention and VA-ECMO implantation in study cohort.

Time Difference	Statistic	Standard Therapy (n=18)	V-A ECMO + Standard Therapy (n=17)
Presenting CGS to initial angiogram (hr)	Median (IQR)	3 (2-5)	2 (1-4)
Presenting CGS to Primary PCI (hr)	Median (IQR)	4 (2-6)	2 (1-4)
Initial angiogram to Primary PCI (min)	Median (IQR)	17 (9-28)	20 (10-30)
Time from onset of CGS to arrival in cath lab (hr)	Median (IQR) Range	1.7 (0.9-3.6) 0.0-12.1	1.6 (1.1-4.6) 0.8-4.9
Time from onset of CGS to balloon/thrombus aspiration (hr)	Median (IQR) Range	1.9 (1.4-3.6) 0.5 – 13.0	2.2 (1.6-4.1) 0.0-5.4
Time from first medical contact to V-A ECMO implantation (hr)	Median (IQR) Range	- -	4.4 (4.2-8.8) 3.2-10.3
Time from onset of CGS to V-A ECMO implantation (hr)	Median (IQR) Range	- -	4.8 (3.7-6.5) 0.8-9.0

Supplementary Table 4. Causes of in-hospital non-cardiovascular death.

	Statistic	Standard Therapy (n=18)	V-A ECMO + Standard Therapy (n=17).
Total number of non-CV death	N	7	5
Causes of Non-CV death			
Hypoxic Brain Injury	n	5	3
Sepsis/Pneumonia	n	2	0
Other*	n	0	2

CV=cardiovascular.

**In the V-A ECMO group, other causes of death include pulmonary haemorrhage (1) and multiorgan failure with lower gastrointestinal bleeding (1).*

Supplementary Table 5. Quality of life at 30-day clinic using the EQ-5D-3L questionnaire.

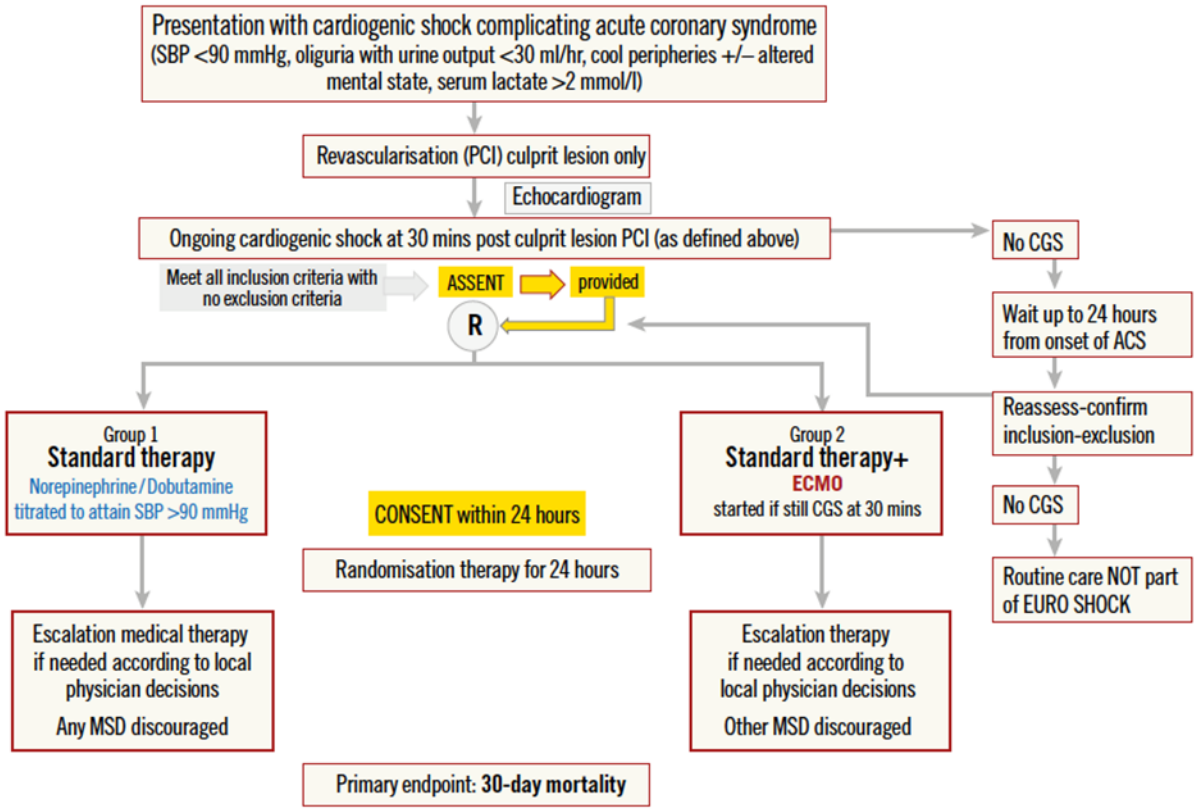
EQ-5D-3L	Statistic	Standard Therapy (n=18)	V-A ECMO + Standard Therapy (n=17)
Patients with 30-day visit performed	N	6	8
Mobility at 30 days			
I have no problems in walking about.	n/N	2/2	2/4
I have some problems in walking about	n/N	0/2	2/4
Self-Care at 30 days			
I have no problems with self-care.	n/N	2/2	2/4
I have some problems washing and dressing myself.	n/N	0/2	1/4
I am unable to wash or dress myself.	n/N	0/2	1/4
Usual activities at 30 days			
I have no problems doing my usual activities.	n/N	2/2	2/4
I am unable to perform my usual activities.	n/N	0/2	2/4
Pain/Discomfort at 30 days			
I have no pain or discomfort.	n/N	0/2	4/4
I have moderate pain or discomfort.	n/N	2/2	0/4
Anxiety/Depression at 30 days			
I am not anxious or depressed.	n/N	1/2	3/4
I am moderately anxious or depressed.	n/N	1/2	1/4
EQ-5D-3L summary index	Median (IQR)	0.765 (0.739-0.790)	0.667 (0.326-1.00)
EQ-5D-3L VAS	Median (IQR)	28 (6-50)	65 (53-75)

VAS=Visual Analogue Scale.

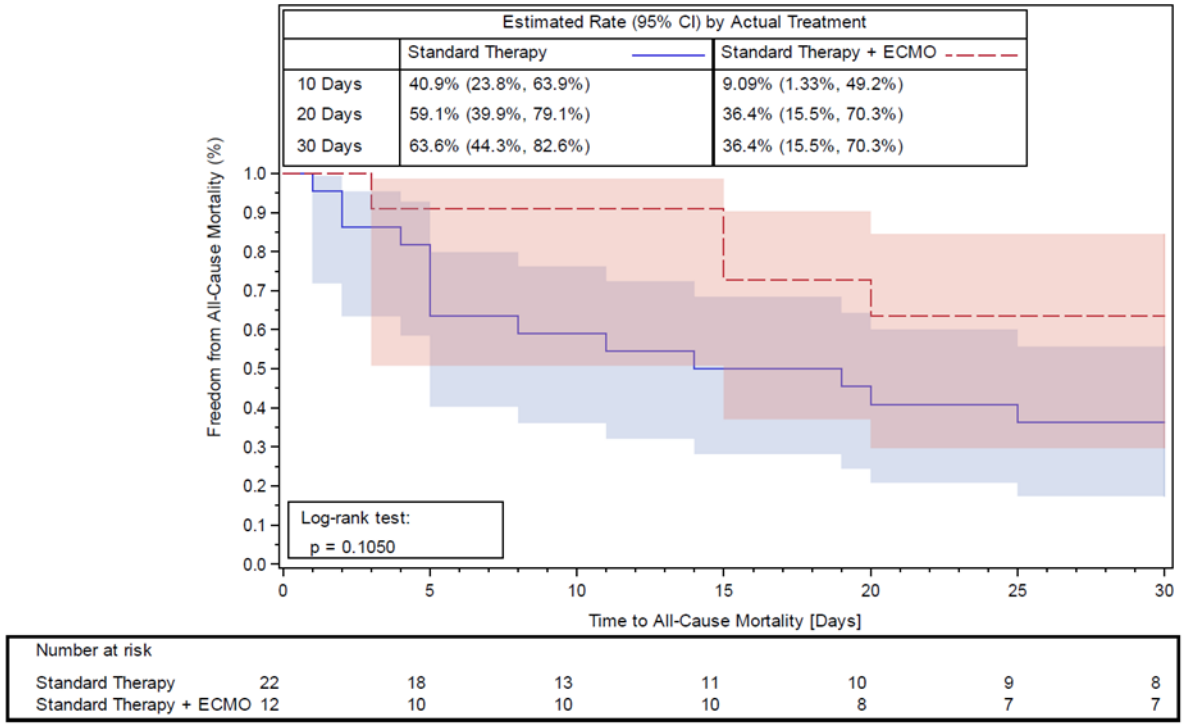
Supplementary Table 6. In-hospital serious adverse events.

In-hospital adverse event	**Statistic**	**Standard therapy (n=18)**	**VA-ECMO + Standard Therapy (n=17)**
Total number of events	N	13	9
Patients with an adverse event	n(%)	5 (27.78%)	6 (35.29%)
CARDIAC	n(%)	4 (22.2%)	5 (29.41%)
• Cardiac arrest	n(%)	1 (5.56%)	1 (5.58%)
• Cardiac tamponade	n(%)	0 (0.00%)	2 (11.76%)
• Ventricular arrhythmia	n(%)	2 (11.11%)	0 (0.00%)
• Ventricular tachycardia	n(%)	0 (0.00%)	2 (11.76%)
• AV block	n(%)	1 (5.56%)	0 (0.00%)
• atrial fibrillation/flutter	n(%)	1 (5.56%)	0 (0.00%)
• LV thrombus	n(%)	0 (0.00%)	1 (5.88%)
RESPIRATORY and THORACIC	n(%)	2 (11.11%)	1 (5.88%)
• Aspiration pneumonia	n(%)	1 (5.56%)	0 (0.00%)
• Pulmonary embolism	n(%)	0 (0.00%)	1 (5.88%)
• Thoracic Haemorrahge	n(%)	1 (5.56%)	0 (0.00%)
INFECTIONS & INFESTATIONS	n(%)	2 (11.11%)	1 (5.58%)
• Post procedural sepsis	n(%)	0 (0.00%)	1 (5.58%)
• Septic shock	n(%)	1 (5.56%)	0 (0.00%)
• Acinetobacter infection	n(%)	1 (5.56%)	0 (0.00%)
GASTROINTESTINAL DISORDERS	n(%)	1 (5.56%)	0 (0.00%)
• Intestinal ischaemia	n(%)	1 (5.56%)	0 (0.00%)
HEPATOBILIARY DISORDERS	n(%)	1 (5.56%)	0 (0.00%)
• Liver Injury	n(%)	1 (5.56%)	0 (0.00%)

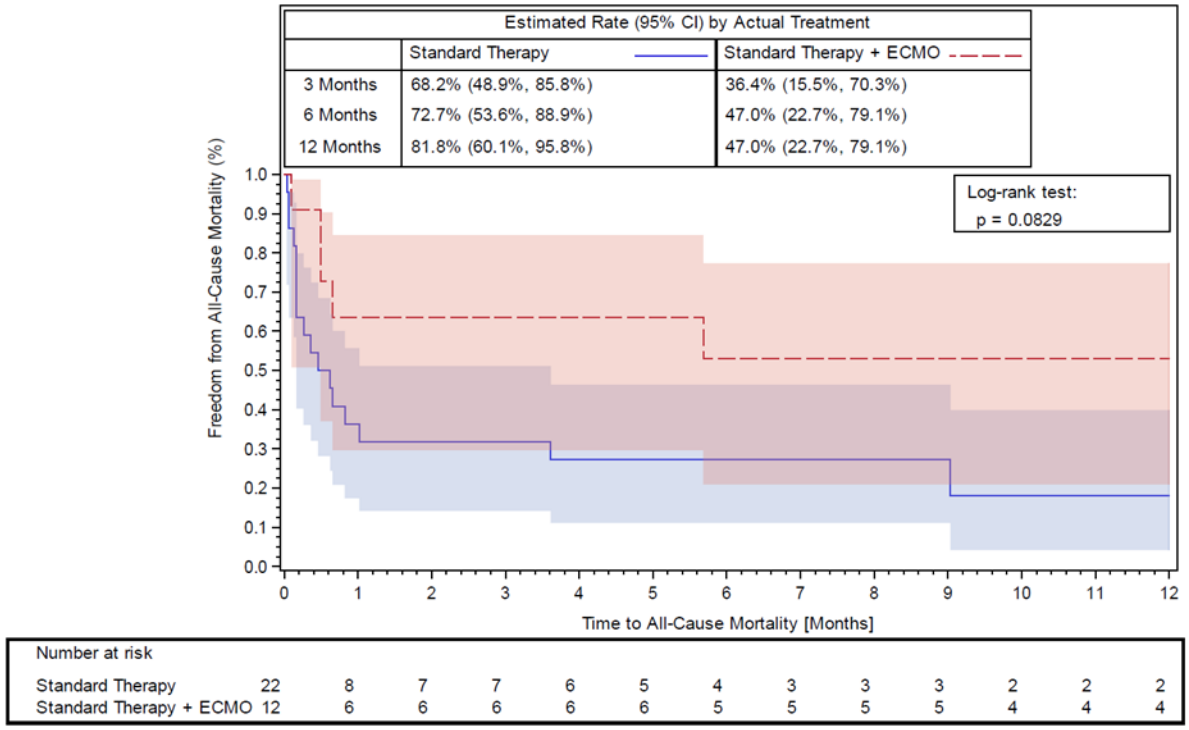
VA-ECMO RELATED SYNDROMES • Harlequin syndrome	n(%) n(%)	NA NA	1 (5.88%) 1 (5.88%)
SURGICAL & MEDICAL PROCEDURES • Heart Transplantation	n(%) n(%)	1 (5.56%) 1 (5.56%)	0 (0.00%) 0 (0.00%)
VASCULAR DISORDERS • Peripheral ischaemia	n(%) n(%)	1 (5.56%) 1 (5.56%)	0 (0.00%) 0 (0.00%)



Supplementary Figure 1. Trial flow diagram for EURO SHOCK.



Supplementary Figure 2. Primary outcome of 30-day all-cause mortality in the "as-treated" population.



Supplementary Figure 3. Secondary outcome of 12-month all-cause mortality in the "as-treated" population.