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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The EURO SHOCK Trial: Design, Aims and Objectives

Randomised comparison of Extra Corporeal Membrane Oxygenation (ECMO) delivered after acute-PCI plus standard of care versus standard of care alone after acute PCI, in patients presenting with Acute Coronary syndrome and Cardiogenic Shock.

Dr Amerjeet S Banning BSc(Hons) MBBS PhD MRCP[1], Prof Dr Tom Adriaenssens MD [2], Prof Colin Berry MB ChB PhD FRCP(Glasg) FACC[3], Dr Kris Bogaerts PhD[4], Dr Andrejs Erglis MD PhD FESC FACC[5], Prof. Klaus Distelmaier MD, PhD, FESC [6], Dr Giulio Guagliumi MD FESC [7], Prof Dr Steven Haine MD PhD [8], Prof Dr Adnan Kastrati MD FESC[9], Prof Dr Steffen Massberg MD PhD[10], Dr. Martin Orban MD [10], Prof Truls Myrmel MD PhD[11], Dr Alain Vuylsteke BSc MA MD FRCA [12], Prof Fernando Alfonso MD, PhD, FESC [13]. Prof Frans Van de Werf ,MD, PhD[2], Prof Freek Verheugt[14] MD, PhD, Prof Marcus Flather MBBS FRCP MBA[15], Prof Manel Sabate MD PhD FESC[16] Prof Christiaan Vrints FESC FACC[8], Prof Anthony H Gershlick BSc MBBS FRCP[1]
A list of study collaborators can be found in the appendix.

Affiliations

1. University of Leicester, University Hospitals of Leicester, Leicester Biomedical Research Centre, UK.
2. University Hospitals Leuven, Belgium and Katholieke Universiteit Leuven, Department of Cardiovascular Sciences, BE.
3. University of Glasgow, Institute of Cardiovascular and Medical Sciences and Robertson Centre for Biostatistics, UK.
4. Katholieke Universiteit Leuven, Department of Public Health and Primary Care, I-BioStat, BE and Universiteit Hasselt, I-BioStat, BE.
5. Paula Stradina Kliniska Universitates Slimnica AS, Department of Cardiovascular Sciences, LV.
6. Medical University of Vienna, Department of Internal Medicine II, Division of Cardiology, Vienna Austria
7. Azienda Ospedalierea Papa Giovanni XXIII, Department of Cardiovascular Sciences, IT.
8. Antwerp University Hospital, Department of Cardiology and University of Antwerp, Department of Cardiovascular Diseases. Belgium
9. Deutsches Herzzentrum München, Department of Cardiology, DE.
10. Medizinische Klinik und Poliklinik I, LMU University Hospital Munich, DE.
11. The Heart and Lung Clinic, University Hospital North Norway, Tromsø, Norway.
12. Royal Papworth Hospital, Department of Anaesthesia and Intensive Care, UK
13. Cardiac Department. La Princesa University Hospital. IIS-IP, CIBERCV, Madrid, ES
14. Heartcenter, Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, The Netherlands
15. University of East Anglia and Norfolk and Norwich University Hospital, Norwich UK
16. Consorci Institut D'Investicacions Biomediques August Pi i Sunyer, Cardiovascular Institute; Hospital Clínic, ES

Corresponding Author:
Prof A H Gershlick
University of Leicester, University Hospitals of Leicester, Leicester Biomedical Research Centre
Email agershlick@aol.com
Tel 00 44116 256 3021

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Classifications:
ACS / NSTE-ACS
Cardiogenic Shock
Acute Heart Failure
Depressed Left Ventricular Function

Abbreviations:

ACS: Acute Coronary Syndrome

ACE: Angiotensin Converting Enzyme

ARB: Angiotensin Receptor Blocker

BARC: Bleeding Academic Research Consortium

BCIS: British Cardiovascular Interventional 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: Extra-Corporeal Membrane Oxygenation

VA-ECMO Veno-arterial Extra-Corporeal Membrane Oxygenation

ECG: Electrocardiogram

eCRF: electronic Case Report Form

EU: European Union

IABP: Intra-Aortic Balloon Counter-pulsation Pump

ICD: Implantable Cardioverter-Defibrillator

ICER: Incremental Cost Effectiveness Ratio

IVRS Interactive Voice Response System

LV: Left Ventricle

MACE: Major Adverse Cardiovascular Events

MSD: Mechanical Support Device

MI: Myocardial Infarction

m-MDT: Mini-Multidisciplinary Team

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

VARC: Valve Academic Research Consortium

VA-ECMO: Veno-Arterial Extra-Corporeal Membrane Oxygenation

Abstract

<u>Background:</u> 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 revascularization but plateaued since the 1990s. Once established, patients with CGS develop adverse compensatory mechanisms that contribute to the downwards spiral towards death, which becomes difficult to reverse.

<u>Methods and Results</u>: The **"EURO SHOCK'** trial will test the benefit or otherwise of mechanical cardiac support using veno-arterial extra-corporeal membrane oxygenation (VA-ECMO), initiated early after acute percutaneous coronary intervention (PCI) for CGS. The trial sets out to randomize 428 patients with CGS complicating ACS, following primary PCI (P-PCI), to either very early ECMO plus standard pharmacotherapy, or to standard pharmacotherapy alone. It will be conducted in 39 European centers. 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 sub-studies will be undertaken.

<u>Conclusions:</u> 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.

Condensed Abstract

Cardiogenic shock (CGS) affects up to 10% of patients suffering ACS. 30-day mortality is reported at approximately 50%. Since the SHOCK trial in 1999, no pharmacological nor intervention/device have impacted on mortality. The **EURO SHOCK** Trial (supported by the EU Horizons 2020 program) will randomize 428 patients with CGS following ACS and PCI in 39 EU centers to either very early intervention with ECMO or to standard treatment only. The primary endpoint is 30-day mortality. Cost/efficacy will be a core component.

Introduction

Cardiogenic shock (CGS) occurs in up to 10% of patients with ACS, and increased over time, possibly due to better organization of prehospital care, STEMI networks, public education and pre-hospital resuscitation. The US National Inpatient Sample Database reported CGS incidence rose from 6.5% to 10.1% from 2003-2010 (1). The UK BCIS audit data report 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% [Appendix Table 1] compared 4% without CGS) (3,4). Furthermore, 30% of CGS survivors develop cardiac 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 (ICD and 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 revascularization (10), no intervention has shown significant benefit, with marginal benefit from use of Norepinephrine or Levosimendan (Figure 1). Most studies on use of mechanical support device (MSD), such as veno-arterial extra-corporeal membrane oxygenation (VA-ECMO) or heart pumps (e.g. Impella^{TM}) have been retrospective, and include patients treated in a refractory shock state. Some non-randomized data suggest early use of MSD may be beneficial (9).

We hypothesize that initiating support prior to adverse compensatory mechanisms will reduce mortality and morbidity. EURO SHOCK will test in a robust prospective randomized controlled trial 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 hemodynamic decline, reduce multi-organ failure, and so reduce mortality. It is cited as an ongoing study in the most recent position paper on cardiogenic shock (11).

EURO SHOCK (NCT03813134) is a prospective randomized, 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.

Trial hypothesis: "Early VA-ECMO following revascularization by PCI in patients with CGS complicating ACS reduces 30-day mortality compared with standard pharmacological support".

The Trial is organized into work packages (see Appendix 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).

Rationale of timing

Some registry data indicate that the earlier MSD is deployed the better. This has led to the concept that "shock-to-support" times be shortened to the point whereby some believe the MSD should be deployed prior to PCI. However, clinicians involved in EURO SHOCK have all seen cases with improvement in hemodynamic parameters following revascularization of the infarct-related artery, now supported by screening data from EURO SHOCK trial. To avoid unnecessary, expensive and potentially harmful use of MSD, the EURO SHOCK trial will only randomize ***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 randomized, pre-revascularization would cause unacceptably delay in PCI, impacting negatively on National audit metrics (e.g. door-to-balloon times).
2. Patient's condition can improve with PCI. Trials that randomize 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 bailout 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 of <90mmHg for at least 30 minutes, or the requirement for vasopressor or inotropic therapy to maintain SBP>90mmHg with clinical signs of pulmonary congestion, plus signs of impaired organ perfusion with at least one of the following manifestations:

- o altered mental status.
- o cold and clammy skin and limbs.
- o oliguria with a urine output of less than 30 ml per hour
- o elevated arterial lactate level of >2.0 mmol per litre on admission.

Screened patients should fulfill all inclusion with no exclusion criteria (Appendix Table 3).

The key inclusion criteria are:

- Willing to provide informed consent/consultee declaration.
- Presentation with a diagnosis of CGS within 24 h 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/sub-acute stent thrombosis ARC definition).
- Acute PCI has been attempted.
- Persistence of CGS (BP ≤ 90 mm Hg, or need for pharmacological support to maintain BP≥ 90 mm Hg) assessed 30 minutes after successful or unsuccessful revascularization of culprit coronary artery.

Key Exclusion Criteria:

- Age <18y and >=90 years.
- Deemed too frail [Canadian frailty score ≥ 5].
- Other causes of shock
- Severe peripheral vascular disease (precluding access and ECMO contra-indicated).
- 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

- 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 Appendix 4.

Sample size and Power Calculations

Data reporting in-hospital/30-days mortality rates in CGS are summarized in Appendix 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. (14) suggests 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 patients included in the study will have at least an intermediate score, especially as only patients with persistent CGS 30 min post-revascularization will be included.

Some non-randomized studies indicate VA-ECMO may reduce 30-day mortality by 30-45% (15,16). A recent meta-analysis suggests 46% reduction in mortality with VA-ECMO compared with IABP alone (17). We judge that a conservative estimate of 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 world-wide 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 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, USA).

Two important studies justify our power calculations. The recent categorization according to 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 (12). 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 (13). Finally, the numbers of patients adjudged to be required by the on-going 4 trials are very similar.

Study Procedures

Consent

Verbal consent will be taken from the patient and witnessed by an independent heath professional.

Patients may not have the capacity to provide informed consent in the acute CGS setting. If so, then 2 options will be considered, according to individual country legal agreements.

1. Declaration from a consultee (relative/friends) 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 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

Randomization

Assessment of the patient will take place up to 30 minutes after culprit-lesion PCI, and irrespective of success, patients will be considered for randomization 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-Multi-Disciplinary 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 randomized (1:1), stratified according to presentation following OHCA, to either continuing pharmacological support or immediate peripheral VA-ECMO implantation. Randomization 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 randomized strategy before strategy failure is deemed to have occurred. In patients randomized 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 mins after completed P-PCI. VA-ECMO will be deployed as soon as possible and no later than 6 hours after randomization, and within 24 hours of CGS diagnosis.

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

Both randomized 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 ICU, they can still be considered for the trial but must be randomized within 24 hours of first diagnosis of CGS and be able to receive ECMO, if so randomized, within 6 hours.

Results

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 randomized. 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 analyzed 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 6 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 Sub-Studies (Appendix 5)

There are two embedded sub-studies in EURO SHOCK

- Cardiac Magnetic Resonance using novel shortened non-breath-holding protocols to evaluate infarct size, micro-vascular obstruction, myocardial hemorrhage, LV systolic function, LV volume (n=180).
- Impact of VA-ECMO membrane lining on platelet function (n=100).

Organisation of the EURO SHOCK Trial

39 centres throughout Europe will recruit to EURO SHOCK, (Appendix 6). Trial committees and Sponsor are outlined in Appendix 7.

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 be immediately referred to the ECMO centre. Those randomized to control arm will receive standard treatment at the site of randomization. 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 1st March 2020 till end June 2020, although not all centres reopened at this time. As of 1st 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.

The most common reason for trial exclusion was improvement in the clinical status of patients at 30 mins 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.

The EURO SHOCK trial has continued to recruit patients while the centres have been opened. With 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 hemodynamic response as optimally and as early as possible could be important in attenuating the "spiral of decline". Mechanical support devices provide hemodynamic support and offering possible solutions. IABP has shown no benefit in CGS (19). Impella^{TM} has shown limited benefit in small retrospective studies (21,22), possibly due to flow rates with older iterations, or due to timing use. Impella^{TM} 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 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 5 trials currently recruiting trials comparing use of MSD with standard therapy in CGS complicating AMI (Table 2). While the inclusion criteria are similar between 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 use of ECMO with its associated costs and complications in patients who may not require it, while still ensuring ECMO is commenced early enough to prevent development of refractory shock and multi-organ failure. Both ANCHOR and ECMO-CS 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, this mostly relates to left ventricular off loading 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 off-loading the ventricle. All ECMO complications are listed as SAEs and will be adjudicated by the Independent CEC who will prepare these for the DSMB who 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 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 available literature. The trial will be open-label, which could lead to systematic bias, however independent adjudication and blinding of endpoint evaluation will mitigate against the effects of this.

Conclusion

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 run to the highest research governance principles.

Impact on Daily Practice

Should EURO SHOCK demonstrate VA-ECMO reduces mortality from ACS CGS, it will lead to guidelines recommendations, and also propose early transfer of CGS patients to ECMO capable centres within “Shock Networks”.

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Appendix

Collaborators:
Jay Gracey[1], Mel Ferguson[1], Jeanette Mueller[2], Philip Bousfield[3], Hakeem Yusuff[1], Cat Taylor [1]
Affiliations
1. University of Leicester, University Hospitals of Leicester, Leicester Biomedical Research Centre, UK.
2. Accelopment AG, Zurich, Switzerland.
3. Chalice Medical, UK.

Conflicts of Interest Statement

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Mr 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. Our involvement in the Euroshock trial is such that the use of our equipment is not actively promoted because centers are encouraged to use whatever ECMO devices they are familiar with and use under their current practice.
All other authors and collaborators have no conflicts of interest to declare.

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Table Headings

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

Table 2: Current major trials assessing use of MSD in Cardiogenic Shock complicating acute myocardial infarction

Main Reason patient not included in the trial	**N (%)**
GCS did not occur within 24hr 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%)
GCS had resolved at 30mins 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%)
OOHCA: no ROSC/pH <7.0/no bystander CPR within 10mins of collapse	8 (15%)
Lactate <2.0mmol/L	1 (2%)
Other	6 (11%)

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

Study	N	Randomisation groups	Primary outcome
EURO SHOCK (NCT03813134)	428	Patients presenting with GCS 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 6hr 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 GCS 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 revascularization 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.

Table 2: Current major trials assessing use of MSD in Cardiogenic Shock complicating acute myocardial infarction.

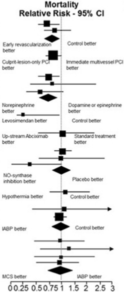
Figure Legends

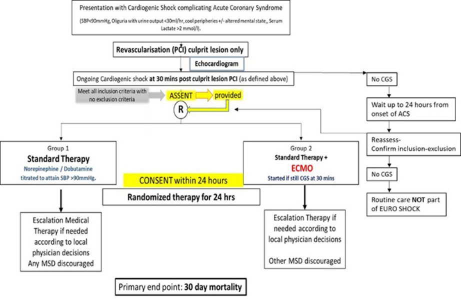
Figure 1:
The effect of assessed interventions on outcomes from cardiogenic shock. Modified from Thiele H et al. *Eur Heart J*, 2019; 40(32): 2671–2683.

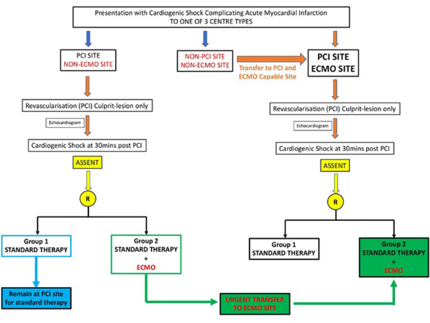
Figure 2:
EURO SHOCK Trial Flow Diagram.

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

Trial	Follow-up	n/N	n/N	Relative Risk - 95% CI
Revascularization (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 revascularization				
CULPRIT-SHOCK	30 days	149/344	176/341	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**	**0.70 (0.54;0.91)**
Inotropes				
Fuhrmann et al.	30 days	5/16	10/16	0.33 (0.11;0.97)
Glycoprotein IIb/IIIa-Inhibitors				
PRAGUE-7	In-hospital	15/40	13/40	1.15 (0.59;2.27)
NO-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**	**1.05 (0.85;1.29)**
Hypothermia				
SHOCK-COOL	30 days	12/20	10/20	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	19/301	123/298	0.96 (0.79-1.17)
Total		**126/319**	**129/319**	**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**	**1.01 (0.71;1.44)**




Presentation with Cardiogenic Shock complicating Acute Coronary Syndrome
(SBP<90mmHg, Oliguria with urine output <30ml/hr, cool peripheries +/- altered mental state,, Serum Lactate >2 mmol/l).
Revascularisation (PCI) culprit lesion only
Echocardiogram
Ongoing Cardiogenic shock at 30 mins post culprit lesion PCI (as defined above)
No CGS
Meet all inclusion criteria with no exclusion criteria
ASSENT
provided
R
Wait up to 24 hours from onset of ACS
Reassess-
Confirm inclusion-exclusion
Group 1
Standard Therapy
Norepinephine / Dobutamine titrated to attain SBP >90mmHg.
Group 2
Standard Therapy +
ECMO
Started if still CGS at 30 mins
CONSENT within 24 hours
Randomized therapy for 24 hrs
No CGS
Routine care NOT part of EURO SHOCK
Escalation Medical Therapy if needed according to local physician decisions
Any MSD discouraged
Escalation Therapy if needed according to local physician decisions
Other MSD discouraged
Primary end point: 30 day mortality


Presentation with Cardiogenic Shock Complicating Acute Myocardial Infarction
TO ONE OF 3 CENTRE TYPES
PCI SITE
NON-ECMO SITE
NON-PCI SITE
NON-ECMO SITE
Transfer to PCI and
ECMO Capable Site
PCI SITE
ECMO SITE
Revascularisation (PCI) Culprit-lesion only
Echocardiogram
Cardiogenic Shock at 30mins post PCI
ASSENT
R
Group 1
STANDARD THERAPY
Group 2
STANDARD THERAPY
+
ECMO
Remain at PCI site
for standard therapy
URGENT TRANSFER
TO ECMO SITE
Revascularisation (PCI) Culprit-lesion only
Echocardiogram
Cardiogenic Shock at 30mins post PCI
ASSENT
R
Group 1
STANDARD THERAPY
Group 2
STANDARD THERAPY
+
ECMO

Appendix 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-e2159.	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-e2168.	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, JAHA 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 revascularization/IABP = 44.6% Early mechanical revascularization/IABP = 33.8%
Goldberg et al, Circ Cardiovasc Qual Outcomes, 2016; 9:117-25.	5,686 patients analyzed 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 hospitalized 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; 7356 [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 revascularization 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. Cath Cardiovasc Interv2018; 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 revascularization 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 Cardio Vasc Anaest 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 Eng J Med 2012; 367:1287-96.	IABP-SHOCK II trial. 300 patients presenting with CS randomized to IABP or no-IABP	30-day mortality = 41.3% in non-IABP group.
Thiele et al. N Eng J Med 2017; 377:2419-2432.	CULPRIT-SHOCK.	30-day all-cause mortality: Multivessel PCI group = 51.6% Culprit-only PCI group = 43.3%
Shah M et al. Circ Heart Failure 2018; 11:e004310.	43212 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(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 Interv 2016; 9:341-351.	Review of trends in management and outcomes of patients with cardiogenic shock from the NCDR CathPCI registry. The patients were analyzed 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 Journal 2019; 65:21-28.	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 Disease 2018; 111:555-563.	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 Failure 2016. 18:1144-52.	Retrospective analysis of elderly patients (defined as age ≥75yrs) presenting with MI and Cardiogenic shock from the FAST MI registry.	1 year mortality in 2010 = 59%.
Lee JM et al. JACC 2018; 71:844-856.	Retrospective analysis from the KAMIR-NIH registry	1-year mortality: Multivessel PCI = 21.3% IRA only PCI = 31.7%

Kunadian et al. JACC 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; 223:412-417.	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. JACC 2017; 69:278-287.	IMPRESS study	30-day Mortality: IABP group = 50%, Impella group = 46%.

Appendix 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 9 work packages (WP):

WP 1: Data Management. Lead: Dr S Keane, Prof I Ford (Glasgow CTU)
WP 2: 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 Proof 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

Appendix 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 h 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/sub-acute 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 >=18yrs and <90yrs.

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 <18yrs 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 contra-indicated)
10. Severe allergy or intolerance to pharmacological or antithrombotic anti-platelet 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.

Appendix 4: Primary and Secondary Endpoints for EUROSHOCK

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 (categorized 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 Enpdoints – 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 (categorized 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, 6 and 12 months)
- Minnesota living with heart failure questionnaire (measured at discharge)

CMR sub-trial endpoints

- infarct size
- micro-vascular obstruction
- myocardial hemorrhage
- Left ventricular systolic function
- Left ventricular volume

Appendix 5: Substudies

CMR Sub-study

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, micro-vascular obstruction, myocardial hemorrhage, LV systolic function, LV volume, renal size, perfusion etc.). Multiparametric cardiovascular MRI, including renal imaging where feasible, will be performed following randomization in up to 30 days as soon as clinically feasible when feasible) and repeated at 6 months. Participation in the CMR sub-study will be confirmed through a feasibility questionnaire. We anticipate that the sub-study 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 sub-study is 180. For a minimum between-group difference in peak circumferential strain of 0.05 and a standard deviation of 0.10, a 2-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 Sub-study

Our Industry partner Chalice Medical Ltd (UK) have incorporated a CE mark propriety coating for its oxygenator. We will test further its impact on platelet activation in a simple small sub-study run by Prof. Stan Heptinstall from ”Plateletsolutions 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 “Plateletsolutions Ltd UK”. Small (5ml) blood samples will be taken from the patients at up to 5 time points before, during and after the clinical procedure for analysis of platelet function. They will be collected using a one tenth volume (0.5ml) of 3.8% (w/v) trisodium citrate dihydrate as anticoagulant. Each sample will be analysed using a kit supplied by Platelet Solution 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

Appendix 6: 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	**Sabate**
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 Universitetetsykehuset Nord Norge	**Myrmel**
Latvia	
0601 Paula Stradina Liniska Universitates Slimnica AS	**Erglis**
Italy	
0701 Azienda Ospedalierea Papa Giovanni XXIII	**Guagliumi**
0702 Azienda Universitaria Ospedaliera Careggi, Firenze	Di Mario

0703 Ospedale San Giovanni Bosco di Torino	Bocuzzi
0704 University Hospital of Bologna Policlinico S. Orsola – Malpighi	Saia

Appendix 7: Trial Committees

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

Trial Committees

- **Steering Committee**
  Chairs: 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 (see Appendix 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 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