References online in supplementary material

Please send final pdf to Derek Hausenloy d.hausenloy@ucl.ac.uk

Title: Effect of remote ischemic conditioning on clinical outcomes in patients presenting with a ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

Standfirst: The rationale and study design for the multicentre randomised controlled CONDI2/ERIC-PPCI study

Aim

Ischemic heart disease (IHD) is the leading cause of death and disability worldwide. For patients presenting with an acute ST-segment elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PPCI), new therapies are required to reduce myocardial infarct (MI) size, in order to preserve left ventricular ejection fraction, prevent the onset of heart failure and improve patient survival. In this regard, remote ischemic conditioning (RIC) using transient ischemia/reperfusion of the arm has been reported to reduce MI size in STEMI patients undergoing PPCI. Whether RIC can improve long-term clinical outcomes in this patient group is unknown, and is investigated in the CONDI2/ERIC-PPCI trial.

Methods

The CONDI2/ERIC-PPCI study is a European multicentre (Denmark, Serbia, Spain, and United Kingdom) randomised controlled clinical trial of 4300 STEMI patients undergoing PPCI. Eligible patients will be randomised to receive either RIC (four-5 min inflations/deflations of cuff placed on upper arm) or control prior to PPCI. The primary endpoint of the study will be cardiac death and heart failure hospitalisation. Secondary endpoints will include rates of all-cause death, coronary revascularisation, re-infarction, stroke at 30 days and 12 months, TIMI flow post-PPCI, ST-segment resolution on ECG, and quality of life. MI size will bedetermined in cardiac enzyme and cardiac MRI sub-studies.

Conclusion

The CONDI2/ERIC-PPCI study will determine whether RIC can improve long-term clinical outcomes in STEMI patients undergoing PPCI.
The CONDI2/ERIC-PPCI trial is registered at www.clinicaltrials.gov (Identifiers: NCT01857414 and NCT02342522).

Key words

remote ischemic conditioning, ST-segment elevation myocardial infarction,
primary percutaneous coronary intervention, cardioprotection.

Introduction
Ischemic heart disease (IHD) is the leading cause of death and disability in Europe and worldwide. In patients presenting with an acute ST-elevation myocardial infarction (STEMI), early myocardial reperfusion using primary percutaneous coronary intervention (PPCI) is the most effective treatment for limiting myocardial infarct (MI) size and improving clinical outcomes. However, despite timely PPCI, the morbidity and mortality of STEMI patients remain significant – as such novel therapeutic strategies are required to reduce MI size in order to preserve left ventricular (LV) ejection fraction, prevent the onset of heart failure and improve patient survival.

In this respect, the heart can be protected against acute lethal ischemia/reperfusion injury (IRI) by applying cycles of brief non-lethal ischemia/reperfusion to an organ or tissue remote from the heart – a phenomenon called remote ischemic conditioning (RIC) [1-3]. Interestingly, RIC can be induced non-invasively by simply inflating and deflating a blood pressure cuff placed on the upper arm, an intervention that has been reported to reduce MI size in several proof-of-concept clinical studies [4-10]. Whether RIC can improve long-term clinical outcomes in this patient group is unknown and is the objective of the CONDI-2/ERIC-PPCI study.

METHODS
Study design
The CONDI2/ERIC-PPCI study is a European (Denmark, Serbia, Spain and UK) prospective randomised controlled clinical trial of 4,300 participants. The study will be conducted in accordance with the Declaration of Helsinki and has been approved by the Ethics committees of the respective countries. All patients will provide informed written consent.

Study population
Inclusion criteria
   i.   Onset of symptoms within 12 hours
  ii.   Age≥18 years
 iii.   Suspected STEMI (ST-elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 millivolt (mV) in men or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads)

Exclusion criteria
   i.   Known ineligibility for PPCI
  ii.   Previous coronary artery bypass graft surgery
 iii.   Myocardial infarction (MI) within the previous 30 days
  iv.   Treatment with thrombolysis within the previous 30 days
   v.   Left bundle branch block (LBBB)
  vi.   Patients treated with therapeutic hypothermia
 vii.   Conditions precluding use of RIC (paresis of upper limb, use of an arterio-venous shunt)
viii.   Life expectancy of less than 1 year due to non-cardiac pathology

Randomisation
Patients will be randomised to either RIC or control. Randomisation will be coordinated centrally via a secure website and will be stratified by centre using random permuted blocks. The PPCI operator, medical staff and the research investigator collecting and analysing the data will be blinded to the treatment allocation.

Trial interventions
An automated CellAegis AutoRIC™ cuff device www.cellaegisdevices.com will be used to deliver the RIC protocol. The RIC and sham RIC intervention will be delivered prior to PPCI and according to local conditions - where ambulance transit times allow, the trial intervention will be delivered in the ambulance (Denmark and Spain), but where ambulance transit times are short the trial intervention will be delivered on immediate arrival at the PPCI center (Serbia and UK).

RIC intervention
An automated autoRIC™ cuff will be placed on the upper arm and inflated to 200mmHg for 5 minutes and then deflated for 5 minutes, a cycle which will be undertaken 4 times in total. For patients presenting with a systolic blood pressure (SBP) ≥175mmHg, a manual blood pressure cuff will be used and inflated to 25 mmHg above systolic blood pressure.

Sham RIC intervention
In sites where the trial intervention is applied on arrival at the PPCI centre (Serbia and UK), an AutoRIC™ cuff visually identical to that used in the RIC protocol will be placed on the upper arm and a simulated RIC protocol applied. Inflation will be simulated and held for 5 minutes, deflation will then be simulated and held for five minutes, a cycle which will be undertaken 4 times in total. For feasibility and logistical reasons, in those patients recruited and randomised in the ambulance no sham RIC control will be delivered (Denmark and Spain).

As the RIC / sham RIC protocol lasts 35 minutes, in cases where the door-PPCI time is less than 35 min, the RIC / sham RIC protocol may overlap with the beginning of the PPCI procedure. Under no circumstances will the RIC protocol delay the onset of PPCI.

Study endpoints
Primary endpoint
The primary endpoint will be cardiac death and heart failure hospitalisation at 12 months. These events will be validated by an independent event validation committee (EVC). Heart failure hospitalisation will be defined as an event that meets the following criteria (in brief)[11]: (i) The patient is admitted to the hospital with a primary diagnosis of heart failure (HF); (ii) The patient exhibits documented new or worsening symptoms due to HF on presentation; (iii) the patient has objective evidence of new or worsening HF; and (iv) the patient receives initiation or intensification of treatment specifically for HF.

Secondary endpoints
i. Rates of cardiac death and heart failure hospitalisation at 30 days.
ii. Rates of all-cause death, coronary revascularization,, re-infarction, stroke at 30 days and 12 months
iii. TIMI flow post-PPCI
iv. ST-segment resolution on 90 minute ECG
v. Enzymatic MI size will be assessed from a 48 hour area-under-the-curve (AUC) high-sensitive Troponin-T (hsTrop-T) using blood samples collected at time 0, 6, 12, 24, and 48 hours in a 400 patient substudy.
vi. MI size will be measured by cardiac magnetic resonance (CMR) scan performed at 6 months in a 250 patient substudy.

Sample size determination
The primary combined endpoint will be cardiac death and heart failure hospitalisation at 12 months. According to the UK NIAP 2008 database, cardiac mortality at 12 months ranged from

5.8%-16.7% depending on the call to balloon time, with the overall 12 month death rate of 8.7% for all PPCI patients. In a recent Danish clinical study post-PPCI, the one-year mortality was 9.4% and the cumulative risk of readmission with heart failure was 8%[12]. In another, non-UK based, clinical study, the incidence of heart failure hospitalisation was 12.7% at 12 months post-PPCI[13]. We have based our power calculations on these published studies, accounting for the marked improvements in clinical outcomes in the contemporary era by using much more conservative event rates. As a conservative estimate we will use a combined cardiac death and heart failure hospitalisation event rate of 11.0% at 12 months for all-comer STEMI patients. We have estimated the effect size to be a 25% relative reduction in the event rate. The rationale for this is based on proof-of-concept clinical studies in which RIC have reported 30% reductions in MI size [4-10]. To demonstrate a 25% reduction in the primary composite endpoint in the RIC-treated group (from 11.0% to 8.25%), with 80% power and at the 5% significance level, will require 1,805 patients per treatment arm which equates to 3,610 patients in total. Therefore, we will need to recruit 4,300 STEMI patients (conservatively allowing for a 15% drop-out rate at 12 months).

Statistical Analysis

A detailed statistical analysis plan will be produced prior to un-blinding of any data. The primary analysis will be a comparison of the cardiac death or heart failure hospitalisation event rate one year after randomisation between the RIC and the control arms of the trial amongst all STEMI patients. Hazard ratios and confidence intervals will be calculated using Cox proportional hazards modelling and Kaplan-Meier curves will be produced. In addition risk differences at one year will also be calculated together with 95% confidence intervals. The results for the individual components of the primary endpoint will also be presented together with other time-to-event secondary endpoints such as cardiac death or heart failure hospitalisation at 30 days. Differences in means (continuous variables) together with 95% confidence intervals will be calculated using linear regression models and analysis of covariance techniques where appropriate. The primary analysis will be performed on an intention-to-treat basis i.e. by including all patients where possible according to the group to which they were randomised irrespective of whether they received the intervention as allocated. A secondary per-protocol analysis will be undertaken including only patients who receive the allocated intervention as intended.

Clinical study monitoring and data management

The Clinical Trials Units at the London School of Hygiene and Tropical Medicine, London, UK and the Department of Cardiology and Department of Clinical Epidemiology, Aarhus University Hospital will oversee the trial. The nominated sponsor of the ERIC-PPCI arm will be University College London, and of the CONDI2 arm will be the University of Aarhus.

Discussion

The phenomenon of RIC was initially described in 1993 by Przyklenk et al [1] in a seminal experimental study demonstrating that the cardioprotective effect of ischemic preconditioning could extend from one coronary artery territory to another. The concept of RIC was then extended to organs and tissue remote from the heart (reviewed in {Hausenloy, 2008 3153 /id}). Its translation into the clinical setting were facilitated by the discovery in 2002 by Kharbanda et al [14] that the RIC stimulus could be induced non-invasively in human volunteers by simply inflating and deflating a blood pressure cuff placed on the upper arm. Since then RIC has been investigated as a cardioprotective strategy in a number of clinical settings including cardiac bypass surgery [15-20], elective PCI [21;22], and stroke [23] with mixed results. Despite intensive

investigation, the mechanisms underlying RIC remain unclear but have been attributed to a neuro-hormonal pathway linking the RIC-treated organ or tissue to the target organ [2;3;24].

RIC has also been investigated in the setting of STEMI in five small proof-of-concept clinical studies [4;6-9]. The first study by Botker et al [4;25] reported that RIC (four-5 minute upper arm cuff inflations and deflations) administered in the ambulance by paramedics on route to the PPCI centre, significantly increased mean salvage index from 0·57 in control to 0.69 with RIC at 30 days (as measured by myocardial single-photon emission computerized tomography (SPECT)). In a post-hoc subgroup analysis of patients presenting with a left anterior descending coronary artery STEMI, myocardial salvage was increased further, and there was a significant reduction in final MI size and improvement in LV ejection fraction at 30 days [4;25]. Interestingly, 4-year follow-up of this patient cohort revealed less all-cause death in those patients given RIC at the time of their PPCI, although this study was not prospectively designed or powered to investigate long-term outcomes[10]. Rentoukas et al [6] demonstrated in 96 patients that RIC (three 4-minute upper arm cuff inflations and deflations) administered at the PPCI centre improved ST-segment resolution and reduced MI size assessed by biomarker release when compared to control. Crimi et al [7] found that RIC administered after PPCI reduced biochemical infarct size and was also associated with an improvement of T2-weighted oedema volume and >50% ST-segment resolution in STEMI patients undergoing PPCI. White et al [8] found that RIC initiated on arrival at the PPCI centre reduced MI size by 27% (measured by CMR) in STEMI patients. Finally, Prunier et al [9] confirmed the MI-limiting effects of RIC, but failed to demonstrate an additive cardioprotective effect with ischemic postconditioning. Therefore, it is well-established that RIC can reduce MI size in STEMI patients treated by PPCI, but whether this beneficial effect translates to improved clinical outcomes is not known and will be investigated in the CONDI2/ERIC-PPCI study.

In conclusion, the CONDI2/ERIC-PPCI study will determine whether limb RIC, a non-invasive low-cost therapeutic intervention can improve long-term clinical outcomes in STEMI patients treated by PPCI.

Derek J Hausenloy*[1,2,3,4], Rajesh Kharbanda*[5], Michael Rahbek Schmidt[6], Ulla Kristine Møller[6], Jan Ravkilde[7], Lisette Okkels Jensen[8], Thomas Engstrøm[9], José Manuel García Ruiz[10], Nebojsa Radovanovic[11], Erica F. Christensen[12], Henrik Toft Sørensen[13], Manish Ramlall[1,2], Heerajnarain Bulluck[1,2], Richard Evans[14], Jennifer Nicholas[14], Rosemary Knight[14], Tim Clayton[14], Derek M Yellon[1,2], Hans Erik Bøtker[6].

*These joint first authors contributed equally to this manuscript.

[1]The Hatter Cardiovascular Institute, Institute of Cardiovascular Science, University College London, London, UK
[2]The National Institute of Health Research University College London Hospitals Biomedical Research Centre, London, UK
[3]National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore.
[4]Cardiovascular and Metabolic Disorders Program, Duke-National University of Singapore, Singapore.

[5] Oxford National Institute of Health Research Biomedical Research Centre, John Radcliffe Hospital, Oxford, United Kingdom

[6]University Hospital Skejby, Aarhus, Denmark

[7]Aalborg University Hospital, Aalborg, Denmark

[8]Odense University Hospital, Odense, Denmark

[9]Rigshospitalet, Copenhagen, Denmark

[10]Hospital Universitario Central de Asturias, Oviedo, Spain

[11]Clinical Center of Serbia, Beograd, Serbia

[12]Emergency Medical Service, Central Region, Denmark

[13]Department of Clinical Epidemiology, Aarhus, Denmark

[14] Clinical Trials Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom

*CONDI2/ERIC-PPCI Study Investigators:

Anthony Mathur (London), Peter O'Kane (Bournemouth), John Greenwood (Leeds), Diana Gorog (Lister), Alisdair Ryding (Norwich), Konrad Grosser (East Kent), Nick Curzen, Andrew Flett (Southampton), Dawn Adamson (Coventry), David Hildick-Smith (Brighton), Julian Gunn (Sheffield), Kai Hogrefe (Kettering), Ian Webb (London), Luciano Candilio (London), James Cotton (New Cross), Kamal Chitkara (Derby), Rob Butler (North Staffordshire), Chiara Bucciarelli-Ducci (Bristol), Stephen Hoole (Cambridge), Reto Gamma (Basildon), Chetan Varma (Birmingham), Vinod Venugopal (Lincoln). Iqbal Malik (London), Kaeng Lee (Birmingham), Ali Dana (Portsmouth)

Corresponding authors:

Prof. Derek J Hausenloy
The Hatter Cardiovascular Institute
University College London
United Kingdom
d.hausenloy@ucl.ac.uk

Prof. Hans Erik Bøtker
Department of Cardiology
Aarhus University Hospital
Skejby Denmark
heb@dadlnet.dk

Conflict of interest

Hans Erik Bøtker and Rajesh Kharbanda are shareholders of CellAegis Inc.

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