

# Effect of Remote Ischaemic preconditioning on Clinical outcomes in patients undergoing Coronary Artery bypass graft surgery (ERICCA study): a multicentre double-blind randomised controlled clinical trial

Derek J Hausenloy,<sup>1,2,3,4\*†</sup> Luciano Candilio,<sup>1†</sup>  
Richard Evans,<sup>5</sup> Cono Ariti,<sup>5</sup> David P Jenkins,<sup>6</sup>  
Shyamsunder Kolvekar,<sup>7</sup> Rosemary Knight,<sup>5</sup>  
Gudrun Kunst,<sup>8</sup> Christopher Laing,<sup>9</sup>  
Jennifer M Nicholas,<sup>5</sup> John Pepper,<sup>10</sup>  
Steven Robertson,<sup>5</sup> Maria Xenou,<sup>1</sup> Timothy Clayton<sup>5</sup>  
and Derek M Yellon<sup>1,2</sup>

<sup>1</sup>Hatter Cardiovascular Institute, Institute of Cardiovascular Science, University College London, London, UK

<sup>2</sup>National Institute for Health Research, University College London Hospitals Biomedical Research Centre, London, UK

<sup>3</sup>National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore

<sup>4</sup>Cardiovascular and Metabolic Disorders Program, Duke–National University of Singapore, Singapore

<sup>5</sup>Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK

<sup>6</sup>Department of Cardiothoracic Surgery, Papworth Hospital, Cambridge, UK

<sup>7</sup>The Heart Hospital, University College London Hospitals NHS Foundation Trust, London, UK

<sup>8</sup>Department of Anaesthetics and Pain Therapy, King's College London and King's College Hospital, London, UK

<sup>9</sup>University College London Centre for Nephrology, Royal Free Hospital, London, UK

<sup>10</sup>National Institute for Health Research Cardiovascular Biomedical Research Unit, Royal Brompton & Harefield NHS Foundation Trust, London, UK

\*Corresponding author

†Derek J Hausenloy and Luciano Candilio are joint first authors

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## Scientific summary

### The ERICCA study

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# Scientific summary

## Background

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the world. Coronary artery bypass graft (CABG) surgery is the revascularisation strategy of choice, particularly in patients with complex CAD or diabetes and/or when aged > 65 years. More recently, higher-risk patients are being operated on because of the ageing population, the more complex CAD being operated on, coexistent comorbidities (including diabetes and hypertension) and the increasing occurrence of combined valve surgery. All of these factors together increase perioperative risk, with a significantly higher incidence of death, stroke and acute kidney injury (AKI) therefore seen in these patients. Another important implication of the increasing risk profile of subjects undergoing CABG surgery is the higher magnitude of perioperative myocardial injury (PMI), which has been recognised as being potentially attributable to a number of pathogenetic factors, the most important of which is ischaemia–reperfusion injury. Ischaemia–reperfusion injury is sustained as a consequence of intermittent aortic cross-clamping, intermittent or continuous administration of cardioplegia, or cross-clamp fibrillation. This can be measured using imaging diagnostic modalities and most importantly with the postoperative rise in serum concentrations of cardiac biomarkers, such as creatine kinase MB and troponin T or I. Studies have demonstrated that a postoperative increase in such cardiac biomarkers is associated with worse short- and long-term clinical outcomes, with increases in morbidity and mortality. Therefore, novel cardioprotective strategies are required to protect these patients to reduce PMI and the incidence of potentially devastating complications including stroke, AKI and death.

In this regard, remote ischaemic preconditioning (RIPC), which describes the phenomenon by which brief episodes of transient ischaemia–reperfusion of an organ or tissue distant from another organ or tissue are able to protect the latter from ischaemia–reperfusion, has emerged as a novel, non-invasive and low-cost intervention capable of reducing PMI in patients undergoing cardiac surgery and therefore improving short- and long-term clinical outcomes in these subjects. Since its description in an animal model by Przyklenk *et al.* in 1993 and its first application in healthy human volunteers by Kharbanda *et al.* in 2002, the concept of RIPC has been applied to different clinical settings including elective cardiac surgery, non-cardiac surgery, elective or primary percutaneous coronary intervention and organ transplantation (Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. Regional ischemic ‘preconditioning’ protects remote virgin myocardium from subsequent sustained coronary occlusion. *Circulation* 1993;**87**:893–9; Kharbanda RK, Mortensen UM, White PA, Kristiansen SB, Schmidt MR, Hoschitzky JA, *et al.* Transient limb ischemia induces remote ischemic preconditioning in vivo. *Circulation* 2002;**106**:2881–3). However, particularly in the context of elective CABG surgery, outcomes from randomised clinical trials have been often discordant and this could be for a number of reasons, including patient characteristics, the clinical setting and the use of concomitant medications. Crucially, the vast majority of these studies were relatively small proof-of-concept trials primarily investigating the potential effects of RIPC on PMI and only a much smaller proportion of studies assessed RIPC implications for clinical outcomes, a finding for which such studies were not sufficiently powered.

We therefore conducted a multicentre randomised sham controlled trial to investigate the effects of RIPC on clinical outcomes in higher-risk patients undergoing CABG surgery with or without valve surgery [the Effect of Remote Ischaemic preconditioning on Clinical outcomes in patients undergoing Coronary Artery bypass graft surgery (ERICCA) trial].

## Objectives

The specific research questions addressed in this trial were:

- Does RIPC improve the combined primary end point of death, revascularisation, stroke and myocardial infarction (MI) in higher-risk patients undergoing CABG surgery with or without valve surgery at 12 months post surgery?
- Does RIPC improve any of these clinical outcomes individually in higher-risk patients undergoing CABG surgery with or without valve surgery at 30 days and 12 months post surgery?
- Does RIPC improve PMI, AKI, inotrope requirement, intensive care and hospital stay duration and quality of life in higher-risk patients undergoing CABG surgery with or without valve surgery?

## Methods

The ERICCA trial recruited 1612 higher-risk [euroSCORE (European System for Cardiac Operative Risk) of  $\geq 5$ ] patients undergoing CABG with or without valve surgery from 30 surgical centres in the UK.

Patients randomised to receive RIPC had a standard blood pressure cuff placed on the upper arm and inflated to 200 mmHg for 5 minutes and then deflated for 5 minutes, a cycle that was performed four times in total. The control group received simulated 5-minute inflations/deflations of a standard blood pressure cuff placed on the upper arm, a cycle that was repeated four times. These interventions were undertaken after the induction of anaesthesia.

The primary analysis compared the rate of major adverse cardiac and cerebrovascular events (MACCE) within 12 months between the RIPC arm and the sham control arm using Cox proportional hazards models. The same time-to-event methods were used to evaluate 30-day MACCE; components of 30-day and 12-month MACCE; and all-cause death at 12 months. To compare subgroups with regard to the effect of treatment on the incidence of MACCE, we included an interaction between treatment group and the subgroup variable in the time-to-event model. The primary analysis was conducted on an intention-to-treat (ITT) basis and included all participants regardless of whether the RIPC or sham control procedure was performed and whether or not CABG (with or without valve) surgery was performed. We also carried out a per-protocol (PP) analysis that was restricted to participants who received the RIPC and sham control protocols as specified and underwent CABG (with or without valve) surgery.

## Results

Between April 2011 and March 2014, 1612 patients undergoing on-pump CABG (with or without valve) surgery with blood cardioplegia were recruited. The treatment groups ( $n = 811$  sham control group,  $n = 801$  in RIPC group) were well balanced in respect of both patient baseline characteristics and surgical details. Use of cardiovascular medications during follow-up was similar in the two treatment groups. There were very few participants lost to follow-up before 12 months [28 (3%) sham control group vs. 19 (2%) RIPC group]. All 1612 patients were included in the analysis of the primary outcome.

The proportion of participants with the MACCE primary end point within 12 months was similar between the groups [26.5% ( $n = 212$ ) RIPC group vs. 27.7% ( $n = 225$ ) control group; hazard ratio (HR) 0.95, 95% confidence interval (CI) 0.79 to 1.15;  $p = 0.58$ ]. We found no difference between the groups in any of the individual components of MACCE (cardiovascular death, MI, stroke and coronary revascularisation).

The results of the PP analysis and ITT analyses were very similar, with little difference in the incidence of MACCE between the intervention groups. In the PP analysis 27.2% ( $n = 188/691$ ) of participants in the RIPC group experienced MACCE within 12 months compared with 28.5% ( $n = 204/717$ ) in the sham

control group (HR 0.95, 95% CI 0.78 to 1.16;  $p = 0.64$ ). No evidence was identified that the effect of RIPC was different between any of the prespecified subgroups, including age, euroSCORE, cross-clamp and bypass times, left ventricular ejection function and diabetes.

In addition, multiple imputation analyses undertaken to account for missing data on the perioperative high-sensitivity troponin T (hsTnT) assay provided no evidence of a reduction in total hsTnT release in the 3 postoperative days (observed 2.0% reduction, 95% CI 9% reduction to 6% increase;  $p = 0.63$ ).

Participants in the RIPC arm had a walk distance on the 6-minute walk test (6MWT) at 12 months that was 23.3 metres further than that of sham control participants (95% CI 2.2 to 44.4 metres); however, only 785 participants completed the 6MWT on one or more occasions and this finding should therefore be interpreted cautiously.

There was no evidence of any effect of RIPC on any of the other secondary end points, including the rate of the combined end point at 30 days, death within 12 months, postoperative atrial fibrillation, AKI, postoperative release of neutrophil gelatinase-associated lipocalin (a marker of renal injury) and duration of intensive care unit and hospital stay.

There was no difference in the rate of adverse events between the RIPC group and the control group, with 364 out of 801 cases (45.4%) compared with 354 out of 811 cases (43.6%) respectively. Understandably, 35 out of 736 patients in the RIPC group (4.8%) compared with 2 out of 760 patients in the sham group (0.3%) experienced skin petechiae at the time of the intervention, albeit with no long-term consequences. A similar proportion in the RIPC and sham control groups experienced adverse events at times other than during the RIPC/sham control intervention [ $n = 318/811$  (39%) vs.  $n = 314/801$  (39%)]: however, none of these events was considered to be related to the intervention.

## Conclusions

Remote ischaemic preconditioning, consisting of four 5-minute cycles of ischaemia–reperfusion of the upper arm, did not improve clinical outcomes in higher-risk patients undergoing elective on-pump CABG with or without valve surgery.

It is possible that RIPC might provide beneficial effects in different clinical settings. In the context of ST segment elevation MI patients treated with primary percutaneous coronary intervention, the magnitude of PMI is substantially greater than for cardiac surgery; in this regard, the CONDI2 (Effect of RIC on Clinical Outcomes in STEMI Patients Undergoing pPCI)/ERIC-PPCI (Effect of Remote Ischaemic Conditioning on Clinical Outcomes in STEMI Patients Undergoing PPCI) trial [see [www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT01857414 and NCT02342522 (accessed 17 March 2016)] will investigate the effect of RIPC on major clinical outcomes in this group of patients. In addition, the recently completed REPAIR (REmote preconditioning for Protection Against Ischaemia–Reperfusion in renal transplantation) trial (ISRCTN30083294) found that RIPC using transient arm ischaemia–reperfusion preserved renal graft function at 12 months following renal transplantation. It is therefore crucial to continue to investigate the potential mechanisms underlying RIPC as this may facilitate the translation of this simple, non-invasive, risk-free, low-cost intervention into beneficial effects on patient outcomes.

## Trial registration

This trial is registered as ClinicalTrials.gov NCT01247545.

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Editorial contact: [nihredit@southampton.ac.uk](mailto:nihredit@southampton.ac.uk)

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