

CLINICAL STUDY PROTOCOL

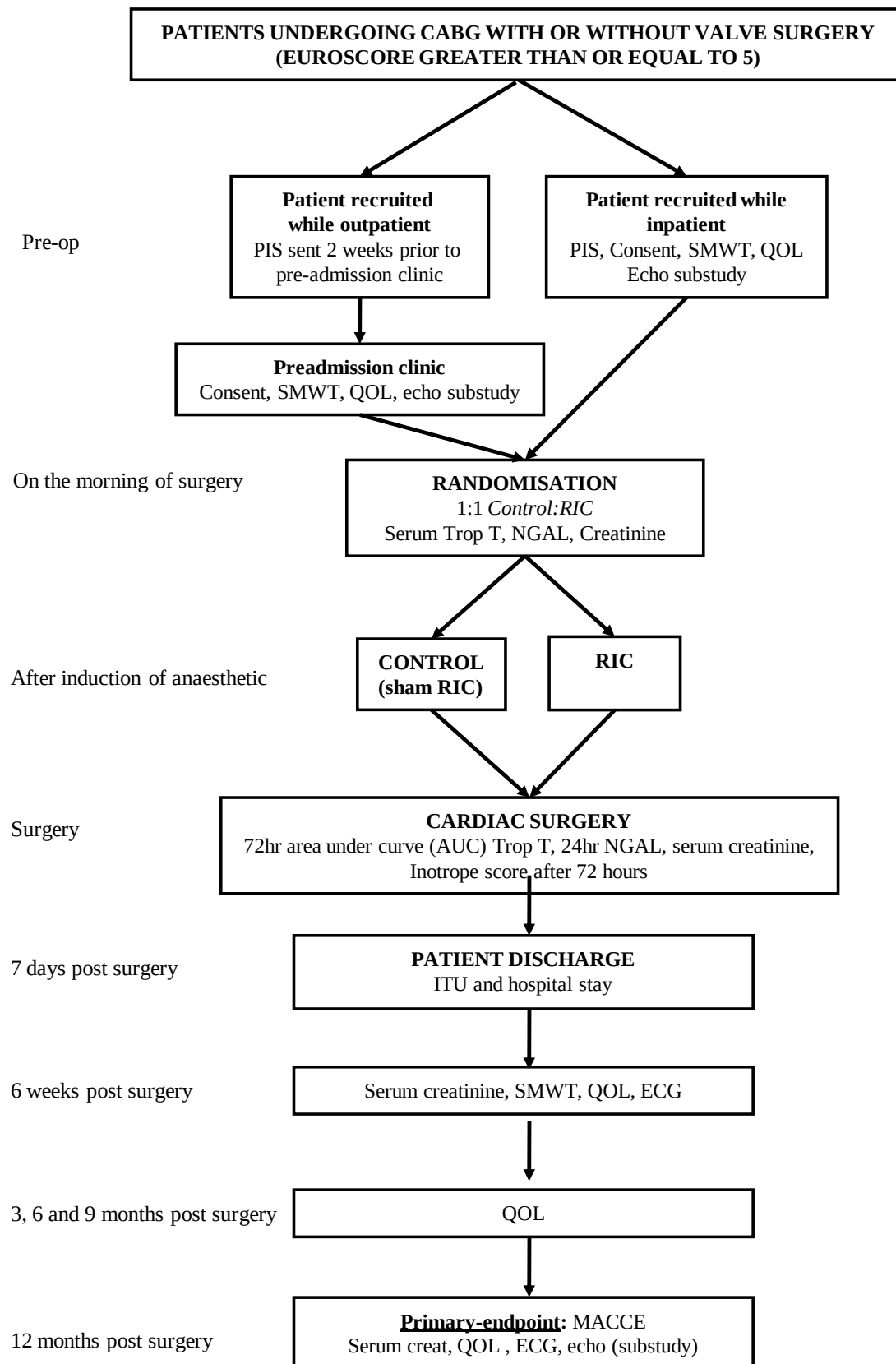
Protocol Number: 12**Study Title:** Effect of Remote Ischaemic preConditioning on clinical outcomes in patients undergoing Coronary Artery Bypass Graft surgery (ERICCA): A multicentre randomised controlled clinical trial**Investigational Product:** N/A**Chief investigator:** Prof Derek J Hausenloy
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1. STUDY SYNOPSIS

Title of clinical trial	Effect of Remote Ischaemic preConditioning on clinical outcomes in patients undergoing Coronary Artery Bypass Graft surgery (ERICCA): A multicentre randomised controlled clinical trial
Sponsor name	University College London Hospital NHS Trust
EudraCT number for proposed trial	N/A
Medical condition or disease under investigation	Cardiac surgery
Purpose of clinical trial	To determine whether remote ischaemic preconditioning (RIC) improves clinical outcomes after cardiac surgery
Primary objective	To determine the effect of RIC on Major Adverse Cardiac and Cerebral Events (MACCE) 12 months after cardiac surgery MACCE include cardiovascular (CV) death, myocardial infarction, revascularisation, and stroke.
Secondary objective(s)	To determine the effects of RIC on: 1. 30 day MACCE 2. All cause death 3. Peri-operative myocardial injury (Troponin T in the first 72 hours post-surgery) 4. Peri-operative renal injury (creatinine and 24 hours serum Neutrophil Gelatinase Associated Lipocalin (NGAL)) post-surgery 5. Length of Intensive Therapy Unit (ITU) stay 6. Inotrope score 7. Hospital stay 8. 6 minute walk test 9. Quality of life 10. Echo Substudy: Left ventricular ejection fraction
Study Design	Randomised double blind placebo-controlled trial
Study End-points	1. CV death, myocardial infarction, revascularisation and stroke 12 months after cardiac surgery 2. 30 day MACCE 3. All cause death 4. 72 hour area under the curve troponin T 5. Acute kidney injury score after 72 hours 6. Creatinine at baseline, 6 weeks and 12 months 7. 24 hour area under the curve NGAL 8. Length of ITU stay 9. Inotrope score after 72 hours 10. Hospital stay 11. 6 minute walk test at 6 weeks and 12 months 12. Quality of life at 6 weeks, 3, 6, 9, and 12 months 13. Substudy: Ejection fraction at 12 months
Sample Size	1610 patients undergoing CABG with or without valve surgery

Summary of eligibility criteria	1. Patients undergoing CABG with or without valve surgery 2. Patients aged 18 years and above 3. Additive Euroscore greater than or equal to 5
Investigational medicinal product and dosage	N/A; this is not a trial of an investigational medical product
Active comparator product(s)	N/A
Route(s) of administration	N/A
Maximum duration of treatment of a subject	N/A
Procedures: Screening & enrolment	All patients undergoing CABG with or without valve surgery will be considered for enrolment
Baseline	Baseline patient data will be recorded.
Treatment period	The intervention is non-pharmacological. Patients will be randomised to one of two groups: control (sham RIC) or RIC. The active treatment will be applied after the induction of anaesthesia and immediately prior to CABG surgery. Active treatment will consist of four 5-minute inflations of a blood pressure cuff on the upper arm to 200mmHg. The inflations will be separated by 5-minute periods when the blood pressure cuff will be deflated. Control treatment (sham RIC) will consist of four 5-minute simulated inflations of a blood pressure cuff placed on the upper arm. The inflations will be separated by 5-minute periods when the blood pressure cuff will be deflated. There is a routine clinical 6 weeks visit and a subsequent research visit at 12 months.
End of Study	Patients will be followed-up for 12months
Procedures for safety monitoring during trial	Serious unexpected adverse event reports will be forwarded to the Clinical Trials Unit, London School of Hygiene and Tropical Medicine (LSHTM). Reports will be made to the Sponsor and the Data Monitoring Committee (DMC). Non-serious unexpected adverse events will be collated and summarised by the Clinical Trials Unit, LSHTM and reported to the DMC.
Criteria for withdrawal of patients on safety grounds	None
Regulatory submissions on safety grounds	Not required as not a CTIMP

2. STUDY FLOW CHART



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3. INTRODUCTION

3.1. Background

Coronary heart disease (CHD) is the leading cause of death in the UK, accounting for 124,000 deaths in 2006 (www.heartstats.org). CHD is estimated to cost the UK economy over £7.9 billion a year, of which 45% is due to direct health care costs (the cost of hospital care and drugs), and 40% attributed to productivity losses (due to CHD mortality and morbidity), and 15% due to the informal care of such patients (www.heartstats.org). As such, improving health outcomes in patients with CHD is a major priority of the NHS as outlined in the National Service Framework for Coronary Heart Disease and embodied in several clinical guidelines and technology appraisals issued by NICE.

Coronary Artery Bypass Graft (CABG) surgery remains the procedure of choice for coronary artery revascularisation in a large number of CHD patients particularly in patients with triple vessel coronary artery disease as highlighted in the recently published SYNTAX study, which demonstrated that CABG surgery is superior to PCI in this patient group (1). About 20,000 first time CABG operations are performed in the UK each year with an overall operative mortality risk of about 1.0% for elective CABG surgery (The Society of Cardiothoracic Surgeons of Great Britain and Ireland National Adult Cardiac Surgical Database Report 2003). Innovative treatment strategies are required to reduce myocardial injury and improve clinical outcomes in patients undergoing CABG surgery, and in this regard, one potential approach is remote ischaemic preconditioning.

3.2. Remote ischaemic preconditioning

Remote ischaemic preconditioning (RIC) describes a phenomenon in which the application of brief episodes of non-lethal ischaemia and reperfusion to an organ (such as the kidney, liver or small intestine) or tissue (such as skeletal muscle) protects the heart against a sustained episode of lethal ischaemia-reperfusion injury (IRI) (2) (reviewed in (3)). The discovery that the RIC stimulus could be reproduced by applying brief episodes of ischaemia and reperfusion to the upper or lower limb (4;5), has facilitated its recent translation from animal studies into the clinical arena.

MacAllister and co-workers (6-8) first demonstrated the concept of RIC in human volunteers using a non-invasive RIC stimulus, comprising inflating a blood pressure cuff applied to the upper arm to 200 mmHg for 5 minutes (to induce brief ischaemia) and deflating the cuff for 5 minutes (to induce brief reperfusion); a cycle which was repeated two more times (6). This RIC stimulus attenuated ischaemia-induced endothelial dysfunction in the contralateral arm arising from a 20 minute episode of sustained cuff inflation (6). Cheung and co-workers (9) were the first to apply this RIC protocol in the clinical arena, in a study in which four-5 minute cycles of lower limb ischaemia and reperfusion reduced myocardial injury, improved airway resistance and decreased inotrope score in children undergoing cardiac surgery. Recently, we demonstrated that three-5 minute cycles of upper limb ischemia and reperfusion reduced myocardial injury (43% reduction in serum troponin-T released over 72 hours) in adult patients undergoing elective coronary artery bypass graft plus or minus valve (CABG with or without valve) surgery (10;11). This last proof-of-concept clinical study forms the pilot data for the current research proposal.

Most recently, RIC using lower limb ischaemia and reperfusion has also been reported to be beneficial in terms of cardiac, renal and neurological protection in the setting of elective surgery for abdominal aortic aneurysm (AAA) (12;13), and surgery for cervical decompression (14). Ali and colleagues (12) demonstrated that invasive lower limb ischemia using two-10 minute episodes of

iliac artery occlusion reduced myocardial injury (as indicated by a 27% reduction in serum troponin-I) and preserved renal function during elective AAA surgical repair. Hoole and co-workers (15) have recently reported that RIC using brief ischaemia and reperfusion of the arm reduced the peri-procedural myocardial injury associated with elective percutaneous coronary intervention (PCI) for stable coronary artery disease (CAD). Finally, Botker and co-workers (16) have recently demonstrated that the RIC using four-5 minute cuff inflations/deflations administered in the ambulance reduced myocardial infarct size in ST-elevation myocardial infarction patients undergoing primary PCI. In the current research protocol, we will be using this particular RIC protocol ie four 5 minute cycles of cuff inflation and deflation.

Therefore, although several proof-of-concept studies have been published, whether RIC can impact on clinical outcomes and improve patient healthcare in higher-risk patients undergoing CABG with or without valve surgery is unknown and is the subject of the current research study.

4. RATIONALE FOR STUDY

The risk profile of patients undergoing CABG surgery continues to change with factors such as (a) the aging population (the proportion of patients over 75 years old has increased by more than 4.5-fold over the last decade with the 5 year mortality in this age group being 35%); (b) the increasing prevalence of diabetes (the proportion of diabetic patients has risen from 15% to 22%, with the operative mortality in this patient group is 2.6%) resulting in an increase in the number of higher-risk patients (which we have defined as an additive EuroSCORE greater than or equal to 5) being operated upon and a corresponding increase in overall operative risk to 5-6%. It has been estimated that at least 80% of patients undergoing CABG surgery in our recruiting centres have an additive EuroSCORE greater than or equal to 5.

These higher-risk patients are at a greater risk of: sustaining peri-procedural myocardial injury; requiring inotropic support post-surgery; experiencing significant acute kidney injury (up to 34% of patients) (17) and experiencing a stroke (1-3%) (18) resulting in worse clinical outcomes. Clearly, new treatment strategies are required to protect the heart, the brain and the kidney during higher-risk CABG with or without valve surgery, such that clinical outcomes can be improved in this patient group. This research proposal investigates a non-invasive virtually cost-free intervention called RIC, which has the potential to improve clinical outcomes in CHD patients undergoing higher-risk CABG with or without valve surgery.

Peri-operative myocardial injury, as measured by serum CK-MB (19), Troponin-T (20-22) or Troponin-I (23-25) during surgery has been associated with worse clinical outcomes post-surgery. Therefore, treatment interventions capable of reducing peri-operative myocardial injury in the setting of CABG with or without valve surgery, may preserve LV (left ventricular) systolic function and improve clinical outcomes. The incidence of acute kidney injury (AKI) following cardiac surgery can be as high as 30% with up to 2% of patients going on to require dialysis (26-28). Even after adjustment for patient co-morbidities and surgical complications of the surgical procedure, the presence of AKI requiring dialysis increases the risk of death 7.9 times compared to those patients not developing AKI (29). Furthermore, it has been reported that changes greater than 0.5 mg/dl (44 mmol/L) in creatinine after cardiac surgery also contribute to a significant increase in mortality at 30 days post surgery (30).

RIC prior to elective surgical repair of an abdominal aortic aneurysm was reported to preserve renal function post-surgery (12;13). Whether RIC is able to preserve renal function in the setting of CABG with or without valve surgery remains to be determined.

We have recently demonstrated in a proof-of-concept clinical study comprising 56 patients that RIC (reviewed in (3)), using three-5 minutes cycles of ischaemia and reperfusion applied to the arm reduced myocardial injury (43% reduction in troponin-T) in a non-selected group of patients undergoing elective CABG with or without valve surgery at the UCLH Heart Hospital (10). We have gone on to demonstrate that the beneficial effect of RIC extends to CABG with or without valve patients receiving cold-blood cardioplegia alone (11).

A similar RIC stimulus can reduce myocardial injury in children undergoing cardiac surgery for congenital heart disease (9), can reduce myocardial and renal injury in patients undergoing surgical repair of an abdominal aortic aneurysm (AAA) (12;13), can reduce neurological injury during cervical decompression surgery (14), can reduce myocardial injury in stable CHD patients undergoing elective PCI (15) or ST-elevation myocardial infarction (STEMI) patients undergoing primary PCI (16).

However, all these clinical trials are proof-of-concept studies, and whether RIC can improve clinical outcomes is unclear. We now intend to determine in a large multi-centre randomised controlled clinical trial whether RIC using brief upper-limb ischaemia and reperfusion can impact on short-term and long-term clinical outcomes in higher-risk patients undergoing CABG with or without valve surgery.

5. TRIAL OBJECTIVES

The single main research question in terms of PICO (Population; Intervention; Comparator; Outcome) is as follows: "In higher-risk adult patients undergoing CABG with or without valve surgery, does RIC induced by brief arm ischaemia and reperfusion, when compared to control, improve clinical outcomes at one year?"

5.1. Primary research objective:

To determine whether RIC improves one year clinical outcomes in patients undergoing CABG with or without valve surgery.

5.2. Secondary research objectives:

1. To determine whether RIC improves 30 day clinical outcomes in patients undergoing CABG with or without valve surgery.
2. To determine whether RIC has an effect on all-cause death.
3. To determine whether RIC reduces peri-operative myocardial injury in higher-risk patients undergoing CABG with or without valve surgery. This will be assessed by measuring serum Troponin T over the 72 hour peri-operative period.
4. To determine whether RIC reduces acute kidney injury (AKI) and preserves renal function post-CABG with or without valve surgery. Previous studies have suggested that RIC can preserve renal function in patients undergoing AAA surgery. Whether RIC has the same effect in higher-risk patients undergoing CABG with or without valve surgery remains unknown. This will be measured by serum NGAL and creatinine and the AKI score.
5. To determine whether RIC improves patient morbidity as measured by ITU stay, inotrope score, the Six minute walk test and Quality of Life assessment.
6. In a substudy of patients recruited via selected hospitals the effect of RIC on LV ejection fraction measured by echocardiography will be assessed.

6. TRIAL DESIGN

6.1. Statement of design

A double-blind randomised trial of the effect of RIC to improve clinical outcomes in patients undergoing CABG with or without valve surgery.

6.2. Number of centres

Patients will be recruited from 30 centres which are listed in Appendix 3 on page 37

The trial will be co-ordinated by the Clinical Trials Unit, London School of Hygiene and Tropical Medicine, London.

6.3. Number of subjects

We estimate a sample size of 1610 subjects will need to be recruited.

6.4. Sample size determination

6.4.1. Primary clinical endpoint

There will be two arms to the trial: control and RIC. We plan to recruit 1610 patients through 30 surgical centres. In the recently published SYNTAX study the MACCE (CV death, myocardial infarction, revascularisation, stroke) rate was 12.4% of patients at 12 months following CABG surgery (1). However, the patients recruited into the SYNTAX study were low-risk with a mean EuroSCORE of 3.8 ± 2.7 , whereas the patients we intend to recruit in our study are higher-risk with EuroSCORE greater than or equal to 5. In another study comprising higher-risk patients defined by them all having left main stem coronary lesions, the MACCE rate (which included some additional neurological criteria) at one year was estimated to be 25% (31). Therefore, for our higher-risk CABG with or without valve patients we have estimated an MACCE rate of 20% at one year, which means that to detect a 27% relative reduction in this primary endpoint in the RIC-treated group (from 20.0% to 14.6%), with a power of 80% and a significance level of 5%, a sample size of 770 patients will be required for each trial arm (1540 in total). A trial of this size would be able to detect an observed relative reduction of 20% (i.e. a risk ratio of 0.8) as statistically significant based on an event rate in the control arm of 20%. To allow for dropouts (4.5% in the SYNTAX study) we plan to recruit 1610 patients in total (805 patients each arm).

6.4.2. Secondary clinical endpoints

We have included sample size calculations for many of the secondary endpoints to demonstrate that for these endpoints we are well-powered.

Please note that the echo substudy requires its own sample size calculation as below.

Inotrope score

In a previous proof-of-concept study, Cheung and co-workers (9) demonstrated that RIC reduced the inotrope score 3 hours post-operatively by 29% in children undergoing corrective cardiac surgery from $11.4 \mu\text{g/kg/min}$ to $8.1 \mu\text{g/kg/min}$. The mean difference was $3.3 \mu\text{g/kg/min}$ with a SD of $4.1 \mu\text{g/kg/min}$ in each group. To demonstrate a similar difference as being statistically significant at the 5% level, with 90% power requires 33 patients per group (66 patients in total).

Myocardial injury (serum Troponin-T)

In our proof-of-concept study, we demonstrated that RIC reduced myocardial injury (measured by 72 hour area under the curve troponin-T) by 43% in patients undergoing CABG surgery from 36.1 µg/L.72hrs to 20.6 µg/L.72hrs (10). The mean difference was 15.5 ng/ml with a pooled SD of 17.8 µg/L. To demonstrate such a difference as being statistically significant at the 5% level, with 90% power, requires 28 patients per group (56 patients in total).

Six minute walk test

In a previous study, cardiac rehabilitation was demonstrated to improve the six minute walk test (6 MWT) by 46% in patients following CABG surgery from 281 metres to 411 metres (32). We conservatively expect to demonstrate a difference a third this magnitude (i.e. 15%). The mean difference would thus be 42 metres with a pooled SD of 99 metres. To demonstrate such a difference as being statistically significant at the 5% level, with 90% power, requires 117 subjects per group (234 in total).

Quality of life

The sample size of 770 patients per treatment group is sufficient to detect even small effects of RIC on QOL at the 12 month follow-up. With 770 patients per group, it will be possible with 90% power to detect an effect size of 0.2 in the EuroQol EQ-5D Health-Related Quality of Life (HRQOL) as statistically significant at the 5% level. This effect size is similar to that found for studies of pacemaker implantation and is at the lower limit of a clinically worthwhile difference (33).

Echo substudy

It is intended to conduct a substudy assessing the impact of RIC on LVEF post-CABG±valve surgery. In a previous study, ischaemic postconditioning (an endogenous cardioprotective strategy similar to RIC) has been reported to improve LVEF by 7% (absolute increase) from 49% to 56% at one year in ST-elevation myocardial infarction patients (34). In order to detect a smaller mean difference of 5% with a common SD of 10. 5% the substudy requires 70 patients in each group (140 in total) using 80% power and a 5% significance level. We will undertake this substudy at a selection of sites.

6.5. Randomisation

6.5.1. Randomisation procedure

As close as possible to the time of surgery, patients will be randomised to one of two groups: either to RIC or to the control. Randomisation will be co-ordinated centrally by the LSHTM CTU via a secure web-site and will be stratified by centre using random permuted blocks. This will only be accessed by the research nurse responsible for performing either the RIC or control protocol. This research nurse will be the only person in each centre aware of the treatment allocation for the patient and he/she will not be involved with the data collection other than those relating to the actual randomisation procedure. The RIC protocol or sham protocol will be performed after the patient has been anaesthetised.

6.5.2. Treatment allocation

Treatment allocations will only be known by one research nurse at each centre. Patients, cardiac surgeons, the research nurse collecting the data, and the assessor of clinical outcomes will be blinded to the treatment allocation.

6.5.3. Recruitment rates

Over the 24 month recruitment period we would expect to recruit approximately 3 high-risk CABG with or without valve patients per month through each of the 30 recruiting centres. Each centre operates on about 5-6 high-risk surgical patients per week, meaning that we would have to recruit at least 25% of the eligible patients. At the time of recruitment for this study there will be no competing studies. In a separate pilot feasibility study of CABG with or without valve patients at one of the recruiting centres we managed to recruit 20 patients in 2 months.

6.6. Study duration and timetable

The anticipated duration will be 4 years. Data collection will occur for up to 1 year after recruitment. There is the possibility of follow-up beyond one year. If this is the case we will involve the NHS Information Centre, the Medical Research Information Service for long-term follow-up.

The total duration of the study will be 48 months.

(1) 0-6 months- Study preparation

- 1.1. Obtain ethical and R&D approval for each recruiting centre (0-2 months).
- 1.2. Staff recruitment (advertising, interviews and training) (0-2 months).
- 1.3. Research protocol publication. Staff training at the 30 recruiting centres (4-6 months).

(2) 6-30 months- Patient recruitment and expected recruitment rates

- 2.1. Patient recruitment (1610 patients in 30 centres) over 24 months.

(3) 7-32 months- 6 week follow-up

- 3.1. Assessment of clinical outcomes.
- 3.2. SMWT
- 3.3. Blood test for creatinine
- 3.4. QOL questionnaire
- 3.5. ECG

(4) 9-39 months- 3, 6, 9 month questionnaire

- 4.1 EQ-5D questionnaire

(5) 18-42 months- One year follow-up

- 5.1. Assessment of clinical outcomes. All data collection should be completed by 42 months.
- 5.2. SMWT
- 5.3. Blood test for creatinine
- 5.4. EQ-5D questionnaire
- 5.5. ECG
- 5.6. Echocardiography (substudy)

(6) 42-48 months- Data analysis

- 6.1. Closing the database, data cleaning and analysis of the data.
- 6.2. Time for production of the draft report.
- 6.3. Dissemination of findings: Publication in a peer-reviewed journal.

6.7. Study objectives

6.7.1. Primary objective

To determine the effect of RIC on major adverse cardiac and cerebral events (MACCE) 12 months after cardiac surgery

6.7.2. Secondary objectives

To determine the effects of RIC on:

1. 30 day MACCE
2. All cause death
3. Peri-operative myocardial injury (Troponin T in the first 72 hours) post-surgery
4. Peri-operative renal injury (creatinine and NGAL and AKI score) post-surgery
5. Length of ITU stay
6. Inotrope score
7. Hospital stay
8. 6 minute walk test
9. Quality of life
10. Substudy: Left ventricular ejection fraction

6.8. Study endpoints

6.8.1. Primary endpoints

CV death, myocardial infarction, revascularisation and stroke 12 months after cardiac surgery

6.8.2. Secondary endpoints

1. 30 day MACCE
2. All cause death
3. 72 hour area under the curve troponin T
4. Acute kidney injury score
5. Creatinine at baseline, 6 weeks and 12 months
6. 24 hours area under the curve NGAL
7. Length of ITU stay
8. Inotrope score
9. Hospital stay
10. 6 minute walk test at 6 weeks and 12 months
11. Quality of life at 6 weeks, 3, 6, 9, 12 months
12. Substudy: Ejection fraction at 12 months

6.9. Trial treatments

The intervention is non-pharmacological. Patients will be randomised 1:1 to one of two groups: control (sham RIC) or RIC. The intervention being assessed is RIC, which refers to the phenomenon in which brief non-lethal episodes of ischaemia and reperfusion in an organ or tissue are able to protect the heart, kidney and brain against a subsequent lethal episode of ischaemia-reperfusion injury (reviewed in (3)). RIC, which will be applied after anaesthesia induction, comprises the inflation of a standard blood pressure cuff, or any other CE approved equipment which becomes available, applied to the upper arm to 200mmHg for 5 minutes and then deflating it for 5 minutes, a cycle which will be repeated 4 times in total. For patients with systolic blood pressures >185mmHg, the cuff will be inflated to at least 15mmHg above the patient's systolic blood pressure. The control group (sham RIC), which will be applied after anaesthesia induction, will also use a standard blood pressure cuff, or any other CE approved equipment which becomes

available. The sham RIC protocol is described as follows: The air valve on the blood pressure cuff is first opened such that the cuff is not inflated on squeezing the attached bulb. The bulb will then be squeezed for a duration of 15 seconds to give the impression that the cuff is being inflated. After 5 minutes the air valve will be closed to give the impression that the cuff is being deflated. After 5 minutes, the air valve will be opened again and the bulb squeezed as before. A cycle which will be repeated 4 times in total. These interventions will be undertaken after the induction of anaesthesia and will not prolong the anaesthetic time or delay the onset of surgery. Recruiting centres will be advised to avoid the routine non-clinical use of intravenous GTN (Glyceryl Trinitrate) during surgery as this agent may interfere with RIC. There are unlikely to be any problems with compliance given that the non-invasive RIC intervention is applied after anaesthesia induction, and is a single intervention administered at one time-point. The drop-out rate has been estimated at 5%-taken into account in sample size calculation. There is a routine clinical 6 weeks visit and a subsequent research visit at 12 months.

6.10. Criteria for Discontinuation

6.10.1. Individual subject

1. Patients are free to choose to withdraw from the trial at any time.
2. Operative complications that directly influence graft revascularisation.

6.10.2. Trial

Unexpected safety issues on the advice of the Data Monitoring Committee

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Inclusion criteria

1. Patients undergoing CABG with or without valve surgery using blood cardioplegia.
2. Patients aged 18 years and above.
3. Patients with an additive Euroscore greater than or equal to 5.

Standard or Additive Euroscore

The Microsoft excel Euroscore calculator (<http://www.euroscore.org/calculators>) will be used to calculate an additive Euroscore for each patient (35). This is an accepted criteria for defining higher-risk patients.

7.2. Exclusion criteria

1. Cardiogenic shock*
2. Cardiac arrest on current admission.
3. Pregnancy.
4. Significant peripheral arterial disease affecting the upper limbs.
5. Patients with significant hepatic dysfunction (INR>2)
6. Patients with significant pulmonary disease (FEV1<40% predicted).
7. Patients with known renal failure with a GFR<30 mL/min/1.73 m².
8. Patients on glibenclamide or nicorandil, as these medications may interfere with RIC.
9. Patients recruited into another study which may impact on the ERICCA study.

**Definition of cardiogenic shock*

Systolic blood pressure <90 mm Hg for 30 minutes before inotrope/vasopressor administration
Or

Vasopressors or IABP are required to maintain systolic blood pressure >90 mm Hg

7.3. Assignment and randomisation number

This will be done on a web-based service through the Clinical Trials Unit at the London School of Hygiene and Tropical Medicine.

7.4. Method of blinding

A research nurse at each study site will remain blinded to the allocation of patients to either real or sham RIC. The preconditioning procedure will be performed by an investigator who is not involved in sample collection or data analysis. The patients and surgeon will be blinded to the treatment allocation.

7.5. Emergency un-blinding

The benign and short-term nature of the intervention makes this an unlikely event. This will be overseen by the Clinical Trials Unit at the London School of Hygiene and Tropical Medicine.

7.6. Subject withdrawal criteria

Withdrawal from the study will be uncommon, because of the benign nature of the intervention, its application within a single 24 hour period, and the embedding of follow-up within routine clinical care.

7.6.1. Criteria for withdrawal from study

Withdrawal of consent by the patients. A patient may decide to withdraw from the study at any time without prejudice to their future care. Withdrawal from the clinical study will be uncommon, because of the non-invasive nature of the planned intervention and the follow-up which will be integrated within routine clinical care wherever possible. We have allowed in our sample size calculation for a drop-out rate of up to 5% (from the SYNTAX trial (1)) although it is expected to be lower than this.

7.6.2. When and how to withdraw subjects from the trial

This can happen at any time pre-, peri- or post-operatively. There are no specific procedures required.

7.6.3. Follow-up of subjects withdrawing from study

Patients who are randomised but withdraw before the intervention will undergo standard clinical care according to local protocols. If patients undergo the intervention but subsequently withdraw, they will undergo standard clinical care. Patients will be encouraged to allow data and samples that have been collected before withdrawal to be used in the analyses. However, if consent to use data/samples is also withdrawn, then these will be discarded. Patients withdrawing from the study will continue to be followed-up by their local team. There should be no need for further follow-up from the research team.

8. TREATMENT REGIMENS

8.1. Remote ischaemic preconditioning protocol

The intervention being assessed is RIC, which refers to the phenomenon in which brief non-lethal episodes of ischaemia and reperfusion in an organ or tissue are able to protect the heart, kidney and brain against a subsequent lethal episode of ischaemia-reperfusion injury (reviewed in (3)). RIC, which will be applied after anaesthesia induction, comprises the inflation of a standard blood pressure cuff applied to the upper arm to 200mmHg for 5 minutes and then deflating it for 5 minutes, a cycle which will be repeated 4 times in total. For patients with systolic blood pressures >185mmHg, the cuff will be inflated to at least 15mmHg above the patient's systolic

blood pressure. The control group (sham RIC), which will be applied after anaesthesia induction, will also use a standard blood pressure cuff, or any other CE approved equipment which becomes available. The sham RIC protocol is described as follows: The air valve on the blood pressure cuff is first opened such that the cuff is not inflated on squeezing the attached bulb. The bulb will then be squeezed for a duration of 15 seconds to give the impression that the cuff is being inflated. After 5 minutes the air valve will be closed to give the impression that the cuff is being deflated. After 5 minutes, the air valve will be opened again and the bulb squeezed as before. A cycle which will be repeated 4 times in total. These interventions will be undertaken after the induction of anaesthesia and will not prolong the anaesthetic time or delay the onset of surgery. There are unlikely to be any problems with compliance given that the non-invasive RIC intervention is applied after the induction of anaesthesia, and is a single intervention administered at one time-point. The drop-out rate has been estimated at 5%- taken into account in sample size calculation.

8.2. Peri-operative Troponin-T

This will be assessed by measuring serum high-sensitive Troponin-T at pre-op and 6, 12, 24, 48, 72 hours (post coming off cardiac bypass) (6 samples per patient collected in a 5ml Vacutainer Tube Serum Separator (SST) or the blood bottle used in the local hospital for measuring Troponin-T). Following elective CABG with or without valve surgery, several studies have demonstrated that myocardial injury, as indicated by the release of the cardiac enzymes Troponin-T and Troponin-I during the peri-operative period, is associated with worse clinical outcomes following surgery (20-25).

Quantitative high-sensitive Troponin T measurement will be performed using a one-step immunoassay based on electrochemiluminescence technology (Elecsys 2010, Roche, Switzerland). The units for reporting to be ng/L. The reference range will be ≤ 14 ng/L (14 ng/L is the 99th centile of ref population with CV risk of $<10\%$). Internal quality control will be performed on a daily basis with external quality control performed every 4 weeks. Each high-sensitive Troponin-T blood sample will be labelled, centrifuged, divided into two samples, aliquoted, frozen (at -20°C) and stored locally. Every quarterly period throughout the 2 year recruitment period batches of samples will be couriered from the 16 recruitment centres to The Doctors' Laboratories in London for analysis.

8.3. Length of ITU/hospital stay and inotrope score

The length of ITU and hospital stay and the inotrope score, are factors which can be influenced by the outcome of surgery and which have an important impact on NHS resources.

The inotrope score provides an objective measurement of the requirement of inotropes in the immediate postoperative period. Data on inotrope use will need to be collected daily from the medical drug chart on the ITU. This was adapted from a study by Ko and co-workers (36) and will be calculated at 0 (time when coming off bypass), 24, 48 and 72 hours after the surgery using the formula below. The inotrope score for the particular timepoint is calculated as follows: at time 0, the inotrope score will be calculated from the dose of the individual inotropes used at the time of coming off bypass. For 24, 48 and 72 hour time-points, the inotrope score will be calculated from the maximum dose of the individual inotropes used in the previous 24 hour period.

Inotrope score = *Dosages (in µg/kg/min) of*
 [Dopamine + Dobutamine + Dopeximine] +
 [(Adrenaline + Noradrenaline + Isoproterenol) x 100] +
 [(Enoximone + Milrinone) x 15]

RIC may impact on these outcome measures by reducing myocardial ischaemic injury, preserving LV systolic function, thereby impacting positively on these outcome measures.

8.4. Peri-operative acute kidney injury

8.4.1. The Acute Kidney Injury Score

The AKI score/grade will be calculated over the 3 day peri-operative period (see table below). Creatinine will be measured daily, and at 6 weeks and one year post-CABG with or without valve surgery. Urine volumes will need to be monitored daily from the fluid on the ITU.

AKI Grade	Creatinine criteria	Urine output criteria
1	A rise of >26.4 µmol/L or 150-200% of baseline	<0.5ml/kg/hr for >6 hours
2	A rise of 200-300% of baseline	<0.5ml/kg/hr for >12 hours
3	An increase of >300%; or creatinine >354 µmol/L with an acute rise of at least of 44µmol/L	<0.3ml/kg/hr for >24 hours or anuria for 12 hours

8.4.2. Neutrophil Gelatinase Associated Lipocalin (NGAL)

Plasma NGAL will be used as an indicator of AKI at the following 4 time-points: pre-operatively, 6, 12 and 24 hours (post coming off cardiac bypass), from which a 24 hours area under the curve will be calculated (4 samples per patient collected in a 5ml SST blood bottle). NGAL is a new early marker for AKI; levels rise rapidly after renal injury and they have been used in cardiac surgery (37;38). The NGAL Rapid ELISA Kit measures human NGAL in plasma/serum. The positive predictive value for acute renal failure is over 90% (37;38).

Each NGAL blood sample will be labelled, centrifuged, plasma divided into two samples, frozen (within 4 hours of collection) and stored locally at -20 °C. Every quarter throughout the 2 year recruitment period batches of samples will be couriered to a single laboratory for analysis (Caltag Medsystems, Buckingham, UK). The samples need to be couriered in dry ice in polystyrene packaging (provided by courier company).

8.5. Left ventricular ejection fraction

A subgroup of 140 patients at a selection of centres will have a transthoracic echocardiogram performed at baseline to assess left ventricular ejection fraction (by bi-planar Simpson's technique and 3D techniques) either in the surgical pre-admission clinic 2 weeks prior to surgery or as an in-patient prior to surgery. This will be repeated at one year (in research outpatient clinic follow-up appointment). LV ejection fraction post-CABG with or without valve surgery is a strong determinant of clinical outcome.

Protocol

Simple and quick echo protocol recording only standard 2D views. (1) Acquisition includes 3 short-axis (SAX) views at mitral valve, papillary muscle and apical levels, and 4 apical views left ventricle (LV) 4-chamber, right ventricle (RV) 4-chamber, LV 2-chamber and LV 3-chamber views. Each cineloop is recorded with conventional grey scale imaging and includes 3 beats. (2) When 3D imaging is available, 2 full volume acquisitions will be acquired during breath holding with 4 beats averaging. LV and LA should be included into the image sector. (3) Detection of severe valvular disease and other abnormalities will be reported. Only recent echo machines from GE and Philips will be used for the study.

Parameters

LV dimensions and LV volumes. LVEF will be assessed by several methods including Teichholz, biplane Simpson's rule and 3D. Global peak systolic strain in radial and longitudinal axis, and mitral annular plane systolic excursion will be obtained. RVEF by fractional area change and tricuspid annular plane systolic excursion will also be obtained (biplane Simpson's rule suffers from large observer variability without contrast).

Analysis

The Echo core laboratory at the Heart Hospital will be in charge of analysis, interpretation, quality control, observer and centre variability, and echo database.

8.6. The Six minute walk test

The 6-minute walk test (6MWT) will be performed at baseline (in the surgical pre-admission clinic 2 weeks prior to surgery), 6 weeks (in outpatient clinic follow-up appointment), and one year (in research outpatient clinic follow-up appointment). Patients will be instructed to walk as far as possible along a straight, flat hospital corridor in 6 minutes. The 6MWT can be used to evaluate the functional status of patients undergoing CABG with or without valve surgery (32). Shortly after CABG with or without valve surgery, functional capacity is significantly reduced, but it rapidly improves after cardiac rehabilitation. This improvement was found to be independent of age, sex, co-morbidities and baseline functional capacity (32).

8.7. Quality of life

The EuroQol EQ-5D Health-Related Quality of Life (HRQOL) questionnaire (www.euroqol.org) will be used to assess patient quality of life post-CABG with or without valve surgery (39), at baseline (in the surgical pre-admission clinic 2 weeks prior to surgery), 6 weeks (in surgical outpatient clinic follow-up appointment), 3, 6 and 9 months (by telephone, email or post) and one year (in research outpatient clinic follow-up appointment). Non-responders will be telephoned.

8.8. Genetic and Biomarker analysis

A 5ml SST sample (to obtain serum for Biomarker testing) and a 5ml EDTA sample (to obtain plasma for Biomarker testing and blood for Genomic testing) will be taken before RIC (or sham RIC) and immediately after RIC (or sham RIC). In the biochemistry or pathology laboratory once the SST blood bottles has clotted the blood sample will be centrifuged at 1300 rpm for 15 minutes and the resultant serum aliquoted into aliquot tubes. In the biochemistry or pathology laboratory the EDTA blood bottles will be centrifuged at 1300 rpm for 15 minutes and the resultant plasma aliquoted into aliquot tubes and frozen at -20°C. The EDTA blood tubes containing the residual blood will then be frozen at -20°C.

Every quarter throughout the 2 year recruitment period batches of samples will be couriered to UCL for analysis. The samples need to be couriered in dry ice in polystyrene packaging (provided by courier company).

9. STUDY PROCEDURES AND ASSESSMENTS

9.1. Selection of patients

At each local hospital, potentially eligible patients according to criteria outlined in section 7 will be selected from two patient groups: (1) Outpatients on the waiting list for CABG with or without valve surgery or (2) Inpatients awaiting CABG with or without valve surgery.

9.2. Informed consent for Outpatients and Pre-admission clinic

Eligible patients identified from outpatient waiting lists for CABG with or without valve surgery at each local hospital will receive a patient information sheet by post informing them of the study, two weeks prior to attending the pre-admission clinic. At the pre-admission clinic, the patient will be seen by the research nurse who will confirm eligibility according to criteria outlined in section 7. Eligible patients will then be recruited and informed consent taken. Baseline data will then be collected.

9.2.1. Baseline data

All patients will have a full medical history taken and a clinical examination as part of usual care. The following are to be recorded:

1. Weight
2. Height
3. Blood Pressure
4. Heart Rate
5. ECG
6. Gender
7. Ethnicity
8. Date of birth
9. Blood Pressure
10. Medical history
 - Diabetes Mellitus
 - Hypercholesterolaemia
 - Hypertension
 - Previous myocardial infarction
 - Previous PCI
 - Previous CABG
 - Previous stroke
 - Atrial fibrillation
 - Peripheral arterial disease
 - Smoking history
 - Family history of IHD
 - Body-mass index
 - NYHA class
 - CCS class
 - Ejection fraction

11. EuroscoreMedication at time of consent
 - Aspirin
 - β-blocker
 - Calcium-channel blocker
 - Nitrates
 - Cholesterol-lowering drug
 - ACE inhibitor/A2 receptor antagonist
 - Insulin
 - Sulphonylurea
 - Metformin
12. Creatinine, Troponin-T and NGAL
13. Blood taken for Genomic, Metabolic and Proteomic analyses (Biomarkers)
14. 6 minute walk test
15. EuroQol EQ-5D
16. Echocardiogram (UCLH Heart Hospital and St Thomas' patients only)

9.3. Informed consent for Inpatients

Patients recruited as inpatients will be given a patient information sheet. The patient should be given sufficient time to consider the trial, recommended to be 24 hours. If the patient agrees to participate in the study informed consent will be obtained. At this point the data and investigations outlined in 9.2. will be collected or performed.

9.4. CABG with or without valve surgery (day 0)

On the morning of surgery the patient will be randomised to receive either RIC or control using a web-based system. The following information on the surgery will be collected.

1. Pre-op ECG
2. Angiogram in last 5 days
3. Post-op ECG
4. Anaesthetic induction
5. Anaesthetic maintenance
6. Type of cardioplegia
7. Bypass time (min)
8. Cross-clamp (min)
9. Number of grafts
10. Valve replaced
11. Complications

9.5. At discharge

The length of ITU and hospital stay, inotrope score will be noted from the medical notes. All blood samples will be timed from when patient definitely comes off bypass. Peri-operative myocardial injury will be noted (serum Troponin-T Pre-op, 6, 12, 24, 48, and 72 hours). Blood NGAL pre-op, 6, 12, and 24 hours and the AKI score determined from the urine volumes and creatinine. On hospital discharge, the patient will be given a Resource-use Diary documenting GP visits, hospital admissions and changes to hospital prescriptions.

9.6. Six weeks out-patient post-CABG with or without valve surgery

Patient will be reviewed in clinical outpatients clinic as per normal procedure.

6 MWT will be performed

Blood test will be taken for creatinine

ECG

Patient will complete EQ-5D questionnaire

Resource diary will be checked and information recorded

9.7. Three, Six and Nine months post-CABG with or without valve surgery

The patient will be contacted and the EQ-5D questionnaire completed over the telephone or sent by post/e-mail to complete and return.

9.8. One year post-CABG with or without valve surgery

Patient reviewed in research outpatient clinic run by the research nurse, as most surgical centres do not routinely follow-up post-CABG with or without valve patients at one year. The GP and hospital medical notes will be reviewed regarding any major cardiac (CV death, MI or revascularisation) or cerebral events (stroke). If the patient is unable to attend an outpatient clinic appointment the one year follow up may be conducted over the telephone.

In addition, the following information will be taken:

- Weight

- Heart rate

- Blood Pressure

- Recording of primary endpoints (see CRF)

- ECG

Blood test taken for creatinine

Echocardiogram will be performed to assess LVEF (substudy)

6MWT will be performed

Patient will complete EQ-5D questionnaire.

Patient will be discharged from the clinical study at one year

Analysis of data

Resource diary will be checked and information recorded

9.9. Study procedures table

	Pre-op		Op	Post-op in hospital				Outpatients				
	Screen	P.Clin or Inpt	Op Day 0	Post -op Day 1	Post -op Day 2	Post- op Day 3	At discha rge	6 wks	3 mths	6 mths	9 mths	12 mths
Clinical Assessments												
Informed consent		X										
Review of inclusion/ exclusion criteria		X										
History and examination		X										
Inotrope score			X	X	X	X						
ITU stay							X					
Hosp stay							X					
Six min walk test		X						X				X
Echo (substudy)		X										X
QOL		X						X	X	X	X	X
Laboratory Assessments												
Creatinine			X	X	X	X		X				X
Troponin T			X Pre-op, 6,12 hr	X 24hr	X 48hr	X 72hr						
NGAL			X Pre-op, 6,12 hr	X 24hr								
Urine volumes			X	X	X	X						
Proteomics		X Pre-op	X PostRIC									
Clinical outcomes												
Death							X	X				X
MI							X	X				X
Revasc							X	X				X
Stroke							X	X				X

10. EVALUATION OF RESULTS

10.1. Response criteria

10.1.1 Biochemical measures

These continuous variables will be measured as described above.

10.1.2 Major adverse cardiac and cerebral endpoints (definitions)

Cardiac events (cardiovascular death, myocardial infarction, repeat revascularisation) and cerebrovascular events (stroke).

Cardiovascular death

This will be defined as death due to a known cardiovascular cause or where the cause of death is unknown i.e. where no other cause of death has been identified from the medical history or an autopsy.

Revascularisation definition

Repeat revascularisation will be defined as any repeat PCI or CABG with or without valve within the first year post-surgery.

Myocardial infarction definition:

Myocardial infarction will include both peri-operative myocardial infarction and myocardial infarction following cardiac surgery. Please send supporting documents (ECG, blood tests for Troponin T or I or CKMB, copy of hospital admission or GP record) to the Clinical Trials Unit at the LSHTM.

Peri-operative myocardial infarction definitions:

Definite peri-operative myocardial infarction (type 5 myocardial infarction)(40) will be indicated by biomarker (Trop T or I) values more than ten times the 99th percentile of the normal reference range during the first 72 hours following CABG with or without valve surgery, when associated with the appearance of new pathological Q-waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium.

A probable peri-operative MI will be recorded if:

- EITHER appearance of new pathological Q-waves or new LBBB on ECG in the absence of biomarkers.
- OR values more than one hundred times the 99th percentile of the normal reference range during the first 72 hours following surgery.

>100 x 99th percentile of the upper reference limit, or upper limit of normal (ULN) has been reported to be associated with 5-10 times relative risk of death.(41)

Post-surgical myocardial infarction definition:

1. A rise and/or fall of Troponin T or I with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:
 - Symptoms of ischaemia
 - ECG changes indicative of new ischaemia (new ST-T changes or new LBBB)
 - Development of Q waves in the ECG
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
 - Probable post-surgical MI will be recorded if there are features suggestive of the above but insufficient evidence to classify as definite MI.
2. Sudden unexpected cardiac death involving cardiac arrest often with symptoms suggestive of myocardial ischaemia and accompanied by presumably new ST elevation or new LBBB and/or fresh thrombus on coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained or at time before the appearance of cardiac troponin T or I in the blood.

Both definite and probable MIs will be included in the MACCE endpoint.

Stroke definition:

Stroke is defined as a focal, central neurological deficit lasting >72 hours which results in irreversible brain damage or body impairment. Probable stroke will be recorded if there are features suggestive of this but insufficient evidence to classify as definite stroke. Please send supporting documents (copy of hospital admission or GP record) to the Clinical Trials Unit at the LSHTM.

Both definite and probable stroke will be included in the MACCE endpoint.

We have used a combined cardiac and cerebral endpoint, as we are investigating the possibility of RIC protecting both the heart and brain during CABG with or without valve surgery. Previous proof-of-concept clinical studies have demonstrated that RIC can reduce myocardial (9;10;12;13) and neurological injury (14) during surgery.

11. ASSESSMENT OF SAFETY**11.1. Definitions**

This is not a trial of an investigational medicinal product. Therefore, by definition all untoward occurrences will be adverse events rather than adverse reactions. Safety assessments will be from time of randomisation to completion of follow up.

11.1.1 Adverse event

This is defined as any untoward medical occurrence affecting a patient which does not necessarily have a causal relationship with the RIC stimulus. The terms “*mild, moderate or severe*” are used to describe the intensity of a specific event or reaction. This is not the same as “*serious*” which is based on patient/event outcome or action criteria as defined below. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or

disease temporally associated with the use of RIC whether or not considered related to the technique.

11.1.2. Serious adverse event (SAE)

Any untoward medical occurrence/effect that:

1. Results in death.
2. Is life-threatening.
3. Requires hospitalisation or prolongation of existing inpatient's hospitalisation.
4. Results in persistent or significant disability or incapacity.

“*Life-threatening*” in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

11.1.3. Unexpected adverse event

This is defined as an adverse event, the nature or severity of which is not consistent with an expected consequence of RIC.

11.2. Expected adverse events (recognised to be caused by the RIC stimulus)

The benign nature of the RIC stimulus excludes there being any expected serious adverse events. The following are expected non-serious events in response to the RIC stimulus and will be recorded on the Case Report Form. They do not need to be reported to the Clinical Trials Unit (see section 11.4).

1. Skin petechiae caused by cuff inflation

11.3. Expected serious adverse events related to usual clinical care

These events are recognised complications of CABG with or without valve surgery. They will be recorded on the Case Report Form but do not need to be reported separately on an SAE form.

1. Death, peri-operative myocardial injury or infarction.
2. Acute renal failure which may require haemodialysis, peritoneal dialysis, or haemofiltration.
3. Atrial fibrillation.
4. Significant heart block requiring temporary or permanent cardiac pacing.
5. Bleeding requiring re-do surgery.

The following events are recognised complications of routine clinical care and for the purposes of this trial will not be designated as SAEs. They do not need to be reported.

1. Complications of surgery, which could include the following:
 - a. Bowel obstruction
 - b. Sepsis
 - c. GI bleed or haematemesis
 - d. Chest infection
 - e. Respiratory failure
 - f. Respiratory tract infection
 - g. Pleural effusion
 - h. Urinary tract infection
 - i. Pulmonary embolism
 - j. Atrial flutter
 - k. Infection of donor site

2. Complications due to administration of anaesthetic agents.
3. Known adverse effects of other drugs used in routine clinical care.

11.4. Reporting unexpected adverse events

Investigators will make their reports of all unexpected adverse events, whether serious or not, to the Clinical Trials Unit, London School of Hygiene and Tropical Medicine.

11.4.1. Unexpected Serious Adverse Events (SAE)

SAEs (other than those described in 11.3) should be reported to the Clinical Trials Unit within 7 days. The report should include an assessment of causality by the Principal Investigator at each site (see section 11.4.4). The Chief Investigator will be responsible for the prompt notification of findings that could adversely affect the health of subjects or impact on the conduct of the trial. Notification of confirmed unexpected SAEs will be to the Sponsor, the Research Ethics Committee and the Data Monitoring Committee (DMC). All deaths will be reported to the sponsor irrespective of whether the death is related to cardiac surgery or is an unrelated event.

11.4.2. Unexpected Non serious adverse events (NSAE)

Unexpected non-serious adverse events should be evaluated by the Principal Investigator. This should include an assessment of causality and intensity (see section 11.4.4) and reports made within 14 days. The Clinical Trials Unit will keep detailed records of all unexpected adverse events reported. Reports will be reviewed by the Chief Investigator to consider intensity, causality, and expectedness. As appropriate these will be reported to the sponsor, the DMC and the Ethics Committee.

11.4.3. Assessment of intensity

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning; the subject is unable to carry out usual activities and/or the subject's life is at risk from the event.

11.4.4. Assessment of causality

Probable: A causal relationship is clinically / biologically highly plausible and there is a plausible time sequence between onset of the adverse event and administration of the intervention.

Possible: A causal relationship is clinically / biologically plausible and there is a plausible time sequence between onset of the adverse event and administration of the intervention.

Unlikely: A causal relationship is improbable and another documented cause of the adverse event is most plausible.

Unrelated: A causal relationship can definitely be excluded and another documented cause of the adverse event is most plausible.

12. STATISTICS

12.1. Study statistician

Statistical analysis will be co-ordinated from the Clinical Trials Unit at London School of Hygiene and Tropical Medicine.

12.2. Statistics

A detailed statistical analysis plan will be produced prior to unblinding of any data. The primary analysis will be a comparison of the MACCE rate one year after CABG with or without valve surgery between the RIC and control arms of the trial. Survival analyses techniques will be used for MACCE and other clinical endpoints. Hazard ratios and confidence intervals will be calculated using Cox proportional hazards modeling and Kaplan-Meier curves produced. The assumptions underlying the Cox model will be assessed. In addition risk differences at one-year together with 95% confidence intervals will be calculated. Differences in means (continuous variables) together with 95% confidence intervals will be calculated using linear regression models and analysis of covariance techniques where appropriate. Analysis will be by intention to treat on all using all available data.

We plan to undertake a limited number of subgroup analyses: these will include age, baseline EuroSCORE, LV ejection fraction, diabetic status, aortic cross-clamp time, cardiac bypass time, Troponin-T or I status at baseline and method of cardioplegia. The subgroups will be analysed using interaction tests.

12.3. Planned interim and sub-group analyses

A DMC will be convened to periodically review data. This will be the only group, along with the statistician producing the reports for the DMC, who will see interim analyses by treatment. The frequency and detail of these analyses will be detailed in a separate DMC charter.

12.4. Number of subjects to be enrolled

We estimate that 1610 subjects will need to be recruited (*see section 6.4 for power calculation*).

12.5. Procedure to account for missing or spurious data

All subjects randomised to the study will be analysed on an intention to treat basis. Data will be validated and the data analysis will take appropriate account of missing values.

12.6. Definition of the end of the trial

The trial shall be considered finished when the last patient recruited reaches the 1-year follow up point. At that point notification of closure of the study will be sent to the Research Ethics Committee.

12.7. Criteria for the termination of the trial

The trial will terminate once the last patient recruited reaches 1 year follow-up.

13. DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

Local investigators shall ensure that all study data are available for trial related monitoring, audits, and research ethics committee review.

14. ETHICAL CONSIDERATIONS

14.1. Consent

All patients will freely give their informed consent to participate in the study. A patient may decide to withdraw from the study at any time without prejudice to their future care. Two weeks prior to attending the pre-admission clinic patients will receive a patient information sheet informing them of the research study. At the pre-admission clinic, informed consent will be undertaken in the surgical pre-admission clinic which takes place 2 weeks prior to CABG surgery. When the patient is considered eligible for recruitment, the research nurse will explain to the patient the clinical study and obtain written informed consent. Only patients that give written consent will be included in the trial. If fully informed consent is not possible, the patient will not be recruited into the study. Patients will be asked to give their consent for their data to be included in a research database.

Inpatients awaiting CABG surgery at the recruiting hospital will be identified by the research nurse who will give the patient an information sheet to read. The patient should be given sufficient time to consider the trial, recommended to be 24 hours, following which informed consent will be taken.

14.2. Declaration of Helsinki and UCL Good Clinical Practice

The study will conform to the spirit and the letter of the declaration of Helsinki, and in accordance with the UCL Good Clinical Practice Guidelines.

14.3. Ethical committee review

East London 3 Research Ethics Committee have reviewed and approved the trial (10/H0701/111). Copies of the letters of approval are to be filed in the study files at each centre. Previous Ethical Approval is already in place to investigate RIC in the setting of CABG with or without valve surgery (REC Ref: 06/20502/83).

15. DATA HANDLING AND RECORD KEEPING

Electronic data will be returned to the London School of Hygiene and Tropical Medicine. Data will be kept for 15 years following completion of the study. The use of the data from the study will be controlled by the chief investigator and the Clinical Trials Unit at the London School of Hygiene and Tropical Medicine. A signed hard-copy of the RIC intervention sheet will be kept at each centre and copied to the Clinical Trials Unit at the London School of Hygiene and Tropical Medicine.

16. INSURANCE

Centres will be covered by NHS indemnity for negligent harm providing researchers hold a contract of employment with the NHS, including honorary contracts held by academic staff. Medical co-investigators will also be covered by their own medical defence insurance for non-negligent harm.

17. PUBLICATIONS POLICY

It is our intention to disseminate the results of the study as widely as possible. This is likely to be through a publication in a peer-reviewed cardiology journal, and through presentations at National

and International Cardiology conferences. Publications will follow the CONSORT guidelines. Authorship will follow international guidelines.

18. RESEARCH GOVERNANCE

The nominated sponsor of our research study is University College London.

18.1. Trial Steering Committee (TSC)

This will comprise Prof David Taggart (chairman), Prof Derek Yellon, Dr Derek Hausenloy, Mr Derek Diamond, Rev Peter Blackburn and Richard Duncker (two previous CABG±valve patients who are service users), Mr Shyam Kolvekar, Prof John Pepper, Dr Chris Laing, Ms Katrine Bavnek (Senior Cardiology Research Nurse), Professor Liam Smeeth, Prof Michael Marber, Mr Tim Clayton and Ms Rosemary Knight. It will meet every 6 months. The TSC will be responsible for drafting the final report and submission for publication.

18.2. Trial Management Group (TMG)

This group will include Dr Derek Hausenloy, Mr Tim Clayton (Senior Medical Statistician), Rosemary Knight (Senior Trials Manager), Mr Steven Robertson (Senior Data Manager) Luciano Candilio (Clinical fellow) and Richard Evans (Clinical Trials Manager). It will meet weekly during the planning stages of the study and less frequently when the study is actually recruiting.

18.3. Data Monitoring Committee (DMC)

Dr Jennifer Nicholas will relay information from TMG to the DMC. The DMC comprises Dr Rajesh Kharbanda (the chair and an independent cardiologist), Mr Adrian Marchbank (an independent cardiothoracic surgeon) and Prof Joan Morris (Professor of Medical Statistics, Queen Mary University of London). It will meet at the start of the trial to establish a DMC charter then at 24, 36 and 48 months to determine if there are any unforeseen effects of RIC.

18.4. Endpoint validation committee (EVC)

The endpoint validation committee comprises Mr Simon Kendall (the chair and an independent cardiac surgeon), Dr Richard Perry (an independent neurologist), and an independent cardiologist, originally Dr Pascal Meier and from April 2013 Dr Alex Sirker. The EVC meets approximately every 6 weeks to validate and adjudicate primary endpoints.

19. References

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APPENDIX 1. Primary Endpoint Definitions:

Cardiac events (cardiovascular death, myocardial infarction, repeat revascularisation) and cerebrovascular events (stroke).

Cardiovascular death

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. Death due to Acute Myocardial Infarction refers to a death by any mechanism (arrhythmia, heart failure, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a “break” (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Death resulting from a procedure to treat a myocardial infarction (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI. Death resulting from a procedure to treat myocardial ischemia (angina) or death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be considered as a death due to other cardiovascular causes.

2. Sudden Cardiac Death refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

- a. Death witnessed and instantaneous without new or worsening symptoms
- b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest AMI
- c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
- d. Death after unsuccessful resuscitation from cardiac arrest
- e. Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)
- f. Unwitnessed death without other cause of death (information regarding the patient’s clinical status preceding death should be provided, if available)

3. Death due to Heart Failure or Cardiogenic Shock refers to a death occurring in the 112 context of clinically worsening symptoms and/or signs of heart failure (see Chapter 7) without evidence of another cause of death and not following an AMI. Note that deaths due to heart failure can have various etiologies, including one or more AMIs (late effect), ischemic or non-ischemic cardiomyopathy, or valve disease.

4. Death due to Stroke refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

5. Death due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories (e.g. dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention (other than one related to an AMI), aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularisation should be classified as cardiovascular deaths.

Revascularisation definition

Repeat revascularisation will be defined as any repeat PCI or CABG with or without valve within the first year post-surgery.

Myocardial infarction definition

Peri operative myocardial infarction is defined as follows:

A rise in Troponin T or I to more than ten times the 99th percentile of the normal reference range during the first 72 hours following CABG with or without valve surgery, when associated with the appearance of new pathological Q waves or new LBBB (left bundle branch block), or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium.

Post surgical myocardial infarction is defined as follows:

A rise and/or fall of Troponin T or I with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischaemia with at least one of the following:

- Symptoms of ischaemia
- ECG changes indicative of new ischaemia (new ST-T changes or new LBBB)
- Development of Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

STEMI (ST-elevation MI)

New ST elevation at the J-point in two contiguous leads with cut off points:

≥0.2 mV in men or ≥0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

NSTEMI (non-ST-elevation MI)

All MIs that are not STEMI are defined as NSTEMI

Stroke definition

Stroke will be defined as a focal neurological deficit of cerebrovascular cause that persists beyond twenty four hours or is interrupted by death within twenty four hours.

APPENDIX 2. Quality of Life Questionnaire:



Health Questionnaire

*English version for the UK
(validated for Ireland)*

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

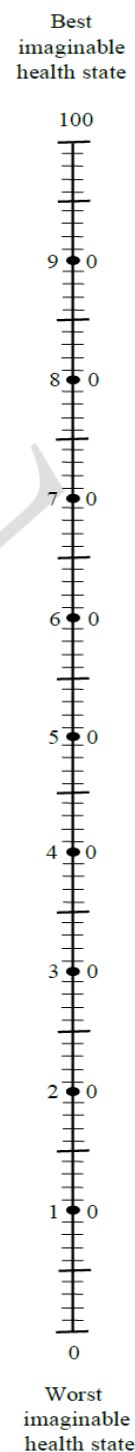
Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**



APPENDIX 3. Local Investigators:

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