ERIC-PPCI

Effect of Remote Ischaemic Conditioning on clinical outcomes in ST segment elevation myocardial infarction patients undergoing Primary Percutaneous Coronary Intervention

Summary Protocol Version 2

Sponsored by UCL

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Introduction

Ischaemic heart disease, the leading cause of death in the UK, accounts for 90,000 deaths per year and costs the UK economy nearly £9 billion per annum. Each year 150,000 patients have an acute myocardial infarction (BHF Stats 2010). In patients presenting with an ST-elevation myocardial infarction (STEMI), early myocardial reperfusion using primary percutaneous coronary intervention (PPCI) is the most effective therapeutic intervention for limiting myocardial infarct (MI) size, a major determinant of prognosis post-PPCI. However, despite PPCI, the morbidity and mortality of STEMI patients remain significant, paving the way for novel therapeutic strategies for protecting the heart against acute ischaemia-reperfusion injury (IRI). In this respect remote ischaemic conditioning (RIC) represents a non-invasive and low cost therapeutic strategy for further reducing MI size, preventing the onset of heart failure, and improving clinical outcomes in PPCI patients.

Remote Ischaemic Conditioning

RIC describes the phenomenon in which the application of multiple cycles of brief 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 from a lethal sustained episode of acute IRI. The discovery that the RIC stimulus could be reproduced by applying brief episodes of ischaemia and reperfusion to the upper or lower limb, has facilitated its recent translation from animal studies to the clinical arena.

In 2002, Kharbanda et al first demonstrated 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. We and others have shown that this RIC stimulus is beneficial in reducing peri-operative myocardial injury in the settings of cardiac bypass and abdominal aortic aneurysm surgery, and reducing peri-procedural myocardial and renal injury in the setting of elective PCI. However, several recent studies have reported neutral findings with RIC in these clinical settings. The reasons for this are unclear but have been attributed to differences in study design, patient selection and concomitant medication (which are known to interfere with RIC cardioprotection). Preliminary data suggest that long term outcomes may be improved in RIC treated CABG patients, although this needs to be confirmed in prospective large randomised controlled clinical trials such as ERICCA and RIPHeart.

RIC and STEMI

RIC has now been investigated in four small proof of concept clinical studies in STEMI patients undergoing PPCI. The first study was published by Botker et al (and 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 the mean salvage index from 0·57 in control to 0.69 with RIC at 30 days (as measured by myocardial SPECT). In a post-hoc subgroup analysis of patients presenting with a left anterior descending 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. Interestingly, 6 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 has not been prospectively designed to investigate long term endpoints. In another study of 96 patients, Rentoukas et al demonstrated that RIC (three 4 minute upper arm cuff inflations and deflations) administered at the PPCI centre improved ST-segment resolution and reduced MI size when compared to control. Crimi et al have found that RIC administered at the onset of myocardial reperfusion was beneficial in STEMI patients undergoing PPCI.

Trial Design

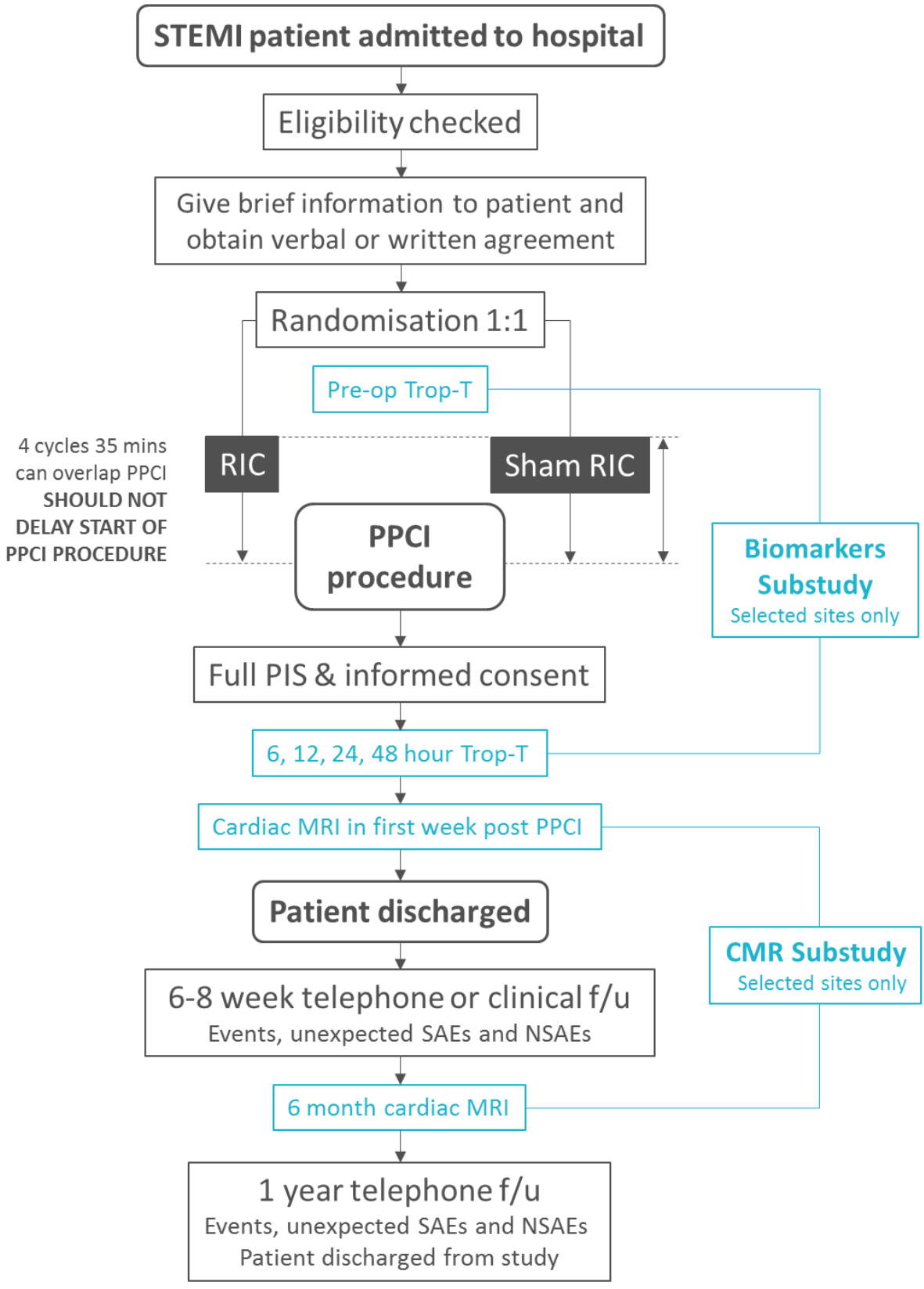
Randomised double blind placebo controlled trial.

Sample Size

2000 patients admitted with a confirmed STEMI and undergoing PPCI.

The trial is a collaboration with the CONDI2 TRIAL (Denmark, Serbia, Spain) which will recruit 2300 patients (NCT01857414). In total the sample size is 4300 patients.

Trial Flowchart



Inclusion Criteria

1. Onset of STEMI symptoms within 12 hours, lasting for more than 30 minutes
2. Patients older than 18 years
3. 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)
4. Eligibility for coronary angiography with follow on PPCI if indicated

Exclusion Criteria

1. Previous coronary artery bypass graft surgery
2. Myocardial infarction (MI) within the previous 30 days
3. Treatment with thrombolysis within the last 30 days
4. Left bundle branch block (LBBB)
5. Patients treated with therapeutic hypothermia
6. Conditions precluding use of RIC (paresis of upper limb, use of an a-v shunt)
7. Life expectancy of less than 1 year due to non-cardiac pathology

Primary Objective

To determine the effect of RIC on cardiac death and hospitalisation for heart failure (HFF) at 12 months in STEMI patients undergoing PPCI.

Secondary Objectives

To determine the effect of RIC on:

1. Markers of successful myocardial reperfusion: ST-segment resolution 90 min post-PPCI, TIMI flow and frame-count post-PPCI, and TIMI blush grade
2. Cardiac death and HHF at 30 days - this data will be collected at the clinical follow up outpatient appointment or by telephone (at 6-8 weeks post-PPCI)
3. Rates of coronary revascularisation, reinfarction, stroke at 30 days and one year
4. Quality of life at one year (EQ-5D-5L)
5. **Biomarkers substudy:** (400 patients at selected sites) 48 hour area under the curve high-sensitivity troponin T
6. **CMR Substudy:** (250 patients at selected sites) Myocardial infarct size expressed as a percentage of the LV mass by Cardiac MRI at 6 months

Trial Treatment

Patients will be randomised on arrival at the hospital and the unblinded research investigator will then deliver either the RIC or sham RIC protocol using an automated CellAegis autoRIC™ cuff device.

RIC

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

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.

The operation of the autoRIC Control Unit with respect to the (simulated) RIC procedure initiation, cycle indication, and termination are identical in the sham device, with the exception that the Applicator Cuff does not inflate.

Duration of Treatment

Although the RIC / sham RIC protocol lasts 40 minutes in total, the cuff should be removed after the 4th cycle of inflation and the last 5 min of reperfusion undertaken with the cuff removed. This means that after 35 mins the intervention is completed. In the cases where the door-PPCI time is less than 35 mins, the RIC / sham RIC protocol may overlap with the beginning of the PPCI procedure when the coronary angiogram is being performed.

Under no circumstances should the RIC / sham RIC protocol delay the onset of the PPCI procedure.

Please refer to the full protocol for details of any references mentioned in this summary. The full protocol is available by emailing ericppci@LSHTM.ac.uk to request a copy.