

Project Title:	Randomized Controlled Trial Comparing Intracoronary Administration of Adenosine or Sodium Nitroprusside to Control for Attenuation of Microvascular Obstruction During Primary Percutaneous Coronary Intervention
Project Ref:	09/150/28
Cost:	£443,778
Lead Applicant & Institution:	Professor Anthony Gershlick University Hospitals of Leicester NHS Trust
Start Date:	01/02/11
Plain English Summary:	<p>Patients with heart attacks are increasingly treated with balloons and stents (angioplasty) to open large arteries blocked by blood clots. Despite removing the blockage, blood flow to the heart muscle may not be fully restored due to poor flow in the small blood vessels of the heart. This 'small vessel obstruction' is variable and often hard to detect but when it occurs is associated with higher rates of repeat heart attacks, heart failure and death. Heart specialists do not know currently how best to limit 'small vessel obstruction'. Strategies to improve blood flow to the heart following angioplasty for a heart attack are very important to reduce death and long term complications.</p> <p>This study will take place at 2 major hospitals in the UK: Glenfield Hospital (Leicester) and Leeds General Infirmary. 297 patients presenting within 6 hours of a heart attack will be allocated randomly to 1 of 3 groups: Group 1. standard angioplasty to serve as control group. Groups 2 and 3 will receive standard therapy and either one of the study's two drugs, both of which may improve blood supply by limiting the amount of small vessel obstruction, given via a very small tube placed beyond the blockage in the affected heart artery (Group 2. adenosine and Group 3. sodium nitroprusside). The effectiveness of the drugs in reducing 'small vessel obstruction' will be assessed using state of the art MRI scanners. MRI can accurately quantify the amount of 'small vessel obstruction' and heart muscle damage that will ultimately form scar tissue. Importantly, the size of the heart attack and the degree of obstruction to blood flow on MRI are strongly related to subsequent complications following a heart attack. Additionally the effect of the drugs on how the 'sticky' cells in the blood function, which contribute to small vessel obstruction, will be assessed.</p> <p>Ethical issues: Heart attacks must be treated very quickly to limit the amount of heart muscle that is damaged and thus patients will be given a short information sheet and be asked to give written assent before being randomly allocated to one of the treatment arms in the study. Patients will subsequently be asked to give fully informed consent for continued participation in the study, on the day following their heart attack. This</p>

	<p>strategy has been used in several studies and allows scientists to investigate new treatments which may save lives in patients with a heart attack.</p>
<p>Abstract:</p>	<p><u>DESIGN:</u> Randomized, controlled, open label trial with blinded endpoint analysis.</p> <p><u>STUDY POPULATION:</u> Patients presenting with P-PCI at 2 major tertiary cardiac centres (Leicester and Leeds). Inclusion criteria: All patients with STEMI eligible for reperfusion by P-PCI. Non culprit disease <70% stenosis at angiography. TIMI flow 0/I. Written informed consent. Exclusion criteria: Contraindications to P-PCI, MRI scanning, contrast agents, or study medications. Age <18 yrs. SBP <90mmHg, cardiogenic shock. Previous Q wave MI. Culprit lesion not identified or located in a by-pass graft. Stent thrombosis. Left main disease. Severe asthma. GFR<30ml/min. Pregnancy.</p> <p><u>INTERVENTIONS:</u> All patients will be treated with bivalirudin and thrombus aspiration and will be randomly assigned, with stratification for symptoms to balloon <3 hrs or >3hrs and anterior MI or not, to one of the following 3 groups: 1) Standard PCI (control). 2) Distal intracoronary (IC) adenosine (300 mcg) via microcatheter (MC). 3) Distal IC SNP (500 mcg) via MC.</p> <p><u>OUTCOME MEASURES:</u> Primary: CMR measured infarct size (IS) at 48-72 hrs post procedure. Secondary: CMR incidence and extent of MVO, myocardial salvage, incidence of haemorrhage, LV volumes and function in the acute stage. Overall Major Adverse Clinical Events (MACE) and its components at 6 months. Angiographic markers of MVO, LV volumes and functions, ECG ST resolution and cardiac enzymes.</p> <p><u>ASSESSMENT AND FOLLOW-UP:</u> Myocardial reperfusion will be assessed using 3T CMR scanners. CMR is the gold standard technique for assessment of MVO and IS, and the quantification of LV mass, volumes and function. CMR analysis will be performed blinded to treatment allocation. Blood samples will be taken from the patients to assess the effect of these treatment agents on platelet activation within the coronary circulation. Follow-up for MACE will be assessed at 6 months.</p> <p><u>PROPOSED SAMPLE SIZE:</u> to detect a 5% difference in infarct size with 90% power, alpha 0.05 and two-tailed, assuming expected infarct size of 20% with a SD 10%, will require 86 pts/group. To allow for dropouts before CMR a total of 297 patients will be recruited.</p> <p><u>STATISTICAL ANALYSIS:</u> Data will be examined for distribution. Groups will be compared by ANOVA, and multivariate analysis will take into consideration possible confounders. Primary analysis will be by intention to treat with a secondary analysis by treatment received. For secondary endpoints, time-to-event regression methods will be used to investigate potentially important predictors of MACE. Initial analyses will adopt a 'complete case' approach, but sensitivity analyses using multiple imputation methods will also be undertaken to assess the plausibility of the 'missing at random' assumption. The study will be monitored by an independent data safety monitoring board. There will be an interim analysis when 5 patients have been included in each arm.</p> <p><u>PROJECT TIMETABLE AND RECRUITMENT RATE:</u> Proposed start date Jan 2011. 297 patients will be recruited in 2 high volume centres. It is estimated to take 18 months to recruit this number of patients (4 patients/week and achieved by both centres in other studies). Follow-up will end in Dec 2012.</p>
<p>ISRCTN:</p>	<p>To follow</p>

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Project Protocol:	To follow
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