Author’s response to reviews

Title: The REFLO-STEMI Trial comparing intracoronary Adenosine, Sodium Nitroprusside and standard therapy for the attenuation of infarct size and microvascular obstruction during primary percutaneous coronary intervention: study protocol for a randomized controlled trial.

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Version: 3 Date: 11 July 2014

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Dear Editors

Timely delivered primary percutaneous coronary intervention (PPCI) in the treatment ST-elevation myocardial infarction (STEMI) has led to sustained morbidity and mortality benefit over the last decade. A major obstacle, however, to reducing major adverse cardiac events (MACE) is sub-optimal perfusion in the microvascular bed despite restoring normal patency in the infarct-related artery (IRA). This is seen angiographically as the “no-reflow” phenomenon and on cardiac magnetic resonance (CMR) imaging as microvascular obstruction (MVO). MVO in its various degrees has been reported to occur in up to 70% of patients with STEMI and is associated with reduced myocardial salvage, increased infarct size, adverse left ventricular (LV) remodelling and higher MACE rates in up to 30% at 1 month and 60% at 12 months. A number of previous studies have investigated the potential of various pharmaco-therapeutic agents to avoid or diminish this challenging phenomenon and indeed whether or not it is possible to do so. However, weaknesses in trial design have produced inconsistent results. Heterogeneity in the studied patient populations, treatments and the outcome measures used have generally hindered systematic review of the data available to draw any meaningful conclusions and therefore weakened the evidence base. The central question of whether MVO can be attenuated or prevented during PPCI for STEMI, and whether this can be translated in to improved clinical outcomes, remains unanswered. This has led to the conception and implementation of our own study, The “REperfusion Facilitated by LOcal adjunctive therapy in STEMI (REFLO-STEMI)” trial, to answer this clinically important question.

The REFLO-STEMI Trial, using a prospective randomised open label blinded endpoint (PROBE) design, will assess whether adjunctive adenosine or sodium nitroprusside (SNP), administered locally to the IRA in theoretically effective doses, impacts on MVO and reduces infarct size (IS) measured optimally with inpatient CMR in patients presenting within 6 hours of onset of STEMI. These vasodilators with pleiotropic effects have shown favourable effects in attenuating MVO, improving myocardial reperfusion and reducing infarct size in previous smaller studies. However, no randomised trial has determined the size of effect with either drug or whether there is a real and quantifiable difference between them.

We believe that our randomised controlled, clinically relevant and important, trial has the potential to inform future STEMI guideline committees. The study has received ethical approval from the National Research Ethics Service. It is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership.

We would like to submit our manuscript as a new ‘Study protocols’ submission to The Trials Journal to facilitate wider dissemination of our trial design through open-access publication. To expedite this process further, given the Trials Journal’s Editorial policy regarding trials with ethical approval and a grant from a major funding body (in our case MRC-NIHR), we would be grateful if the Editors would consider publication without the need for peer-review. The ethics approval letter has been uploaded with this submission and proof of funding for the study can be found at, http://www.nets.nihr.ac.uk/projects/eme/0915028, on the NIHR website outlining the project and funding.

The manuscript has been written as per your guidelines.
There are no competing interests or disclosures for any of the authors.

We would be happy to provide any further information that you may require.

We hope that our study protocol for the REFLO-STEMI Trial finds a home in your journal.

With kind regards,

Sheraz A Nazir  
(Submitting author, on behalf of the authors)