The REFLO-STEMI (REperfusion Facilitated by LOcal adjunctive therapy in ST-Elevation Myocardial Infarction) trial: a randomised controlled trial comparing intracoronary administration of adenosine or sodium nitroprusside with control for attenuation of microvascular obstruction during primary percutaneous coronary intervention

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Scientific summary

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Background

Outcomes following primary percutaneous coronary intervention (PPCI) for ST-elevation myocardial infarction (STEMI) have improved incrementally through the implementation of evidence-based practice. Challenges to attaining very low major adverse cardiovascular event (MACE) rates remain, however. One issue may be suboptimal microvascular perfusion despite restoration of normal patency in the infarct-related artery (IRA). This microvascular obstruction (MVO) occurs in at least 40–70% of STEMI patients, impacts negatively on left ventricular (LV) recovery and leads to worse clinical outcomes independently of infarct size. A number of pharmacological therapies should in theory attenuate MVO severity, with adenosine and sodium nitroprusside (SNP) being the most studied agents. However, heterogeneous trial design and lack of a sensitive method to detect MVO have led to conflicting results and weakened the evidence base.

Objectives

The aim of our REperfusion Facilitated by LOcal adjunctive therapy in ST Elevation Myocardial Infarction (REFLO-STEMI) trial was to assess whether adjunctive adenosine or SNP, administered locally to the IRA in theoretically effective doses, attenuates MVO and reduces infarct size, measured optimally with inpatient cardiac magnetic resonance (CMR) imaging.

Design

The REFLO-STEMI trial was a prospective, multicentre, randomised controlled, open-label trial with blinded end point analysis testing to determine whether intracoronary (IC) adenosine 1–2 mg or SNP 250 µg pre and post stenting compared with standard PPCI reduces infarct size and MVO measured by CMR imaging undertaken 24–96 hours after revascularisation. Clinical follow-up was at a median of 6 months. The primary end point was infarct size (% total left ventricular end-diastolic mass; %LVM) on CMR imaging. CMR scans were read centrally with the readers blinded to treatment and clinical information.

Study population

All patients presenting within 6 hours of onset of STEMI at four regional tertiary cardiac centres (Leicester, Leeds, Newcastle and Coventry) were potentially eligible.

Participants

Patients aged $\geq$ 18 years with STEMI $\leq$ 6 hours from symptom onset requiring PPCI with < 70% stenosis in any non-IRAs and Thrombolysis in Myocardial Infarction (TIMI) flow grade (TFG) 0/1 at baseline angiography were eligible. Patients were excluded if they had any of the following: (1) contraindications to PPCI, CMR scanning, contrast agents or study medications, (2) systolic blood pressure < 90 mmHg or cardiogenic shock, (3) previous Q wave myocardial infarction (MI), (4) culprit lesion not identified or located in a bypass graft, (5) stent thrombosis, (6) left main stem disease, (7) severe asthma, (8) estimated glomerular filtration rate (eGFR) < 30 ml/minute/1.73 m^2 and (9) pregnancy.

Interventions

All patients were treated with bivalirudin (0.75 mg/kg bolus plus infusion of 1.75 mg/kg/hour) and thrombus aspiration. They were randomly assigned (using an independent computerised telephone randomisation service), with stratification for symptoms to balloon time of < 3 hours or > 3 hours and anterior MI or not, to one of the following three groups: (1) standard PPCI (control), (2) distal IC adenosine (1 mg) via the thrombectomy catheter following thrombus aspiration with a second IC dose (1 mg if IRA is right coronary artery or 2 mg if IRA is left coronary artery) following stent deployment via the guide catheter or (3) IC SNP (250 µg) pre and post stenting (second dose via guide catheter). All patients received standard medical care following PPCI.

Outcome measures

Primary

The primary outcome was CMR-measured infarct size (%LVM) at 48–72 hours post PPCI.

Secondary

Secondary outcomes were CMR incidence and extent of MVO (hypoenhancement within the infarct core); myocardial salvage; incidence of haemorrhage; LV volumes and function in the acute stage; angiographic markers of microvascular perfusion [corrected TIMI frame count (cTFC)and TIMI myocardial perfusion grade (TMPG)]; incidence of complete (> 70%) and degree of ST-segment resolution (STR); enzymatic infarct size; and overall major adverse cardiac events (MACEs) and their components at 1–6 months.

Results

In total, 247 patients were randomised, with 222 patients (89.9%) consenting to CMR imaging post PPCI. A total of 207 patients (83.8%) had CMR attempted and 197 patients (79.8%) completed CMR for the primary outcome measure of CMR-derived infarct size.

There were no differences in baseline characteristics between those who were randomised and those who completed CMR imaging. Groups were generally well matched. A reduced incidence of hypercholesterolaemia and statin use was observed in the control (standard PPCI without adjunctive pharmacotherapy) arm. There was also a trend towards a greater incidence of diabetes in the SNP treatment arm. Groups were well matched for infarct territory and, in particular, for anterior MI (randomisation stratified).

A high rate of use of radial vascular access and drug-eluting stents was noted in this contemporary PPCI study. Thrombectomy was mandated as a precursor to drug delivery and the slightly lower thrombectomy use observed in the control arm was not statistically significant. Intraprocedural complications were similar across all groups. However, the incidence of transient atrioventricular (AV) block not requiring pacing was greater in the control arm. There was a low incidence of AV block requiring pacing in this study (2.4% vs. 1.3% vs. 0% in the adenosine, SNP and control arms, respectively). A significantly higher rate of transient hypotension [not requiring vasopressor or intra-aortic balloon-pump (IABP) support] was observed in the SNP arm ($p = 0.028$). Other complications were as expected as a consequence of STEMI and were similar across the groups. There was no statistically significant difference in enzymatic infarct size between the groups.

The incidence of angiographic slow-flow or no-reflow (TFG < 3 or final visual TMPG 0–1) was low and similar across groups and was consistent with the quantitative angiographic [myocardial blush grade (MBG) and cTFC] and electrocardiographic (STR > 70%) assessment of microvascular tissue perfusion. There were no statistically significant differences between these markers of MVO post PPCI.

There was no statistically significant difference in the primary outcome measure of unadjusted infarct size LVM between the adenosine- or SNP-facilitated PPCI group and the control group. Infarct location was the only confounder associated with infarct size. On multivariable regression analysis, adjusting for significant confounders, there was a trend towards a significant increase in mean infarct size in the adenosine group [mean difference 2.73, 95% confidence interval (CI) –0.18 to 5.64; $p = 0.066$] compared with the control group. This was not seen in the SNP group.

Microvascular obstruction was present on late gadolinium enhancement (LGE) images (late MVO) in 67% of patients. The presence of late MVO was significantly higher in the SNP arm than in the control arm (75.4% vs. 56.9%; $p = 0.029$). However, there was no statistically significant difference in quantitative late MVO between the two groups ($p = 0.244$). Quantitatively, late MVO appeared to be higher in the adenosine-treated arm than in the control arm, although, again, this was not statistically significant. Other CMR imaging parameters of microvascular injury were similar between the groups. For both early and late MVO, none of the potential confounders was identified as being of statistical importance by the forward selection procedure.

An increase in LV volumes was observed in the adenosine arm compared with the control arm and this was accompanied by a borderline significant reduction in ejection fraction. LV volumes and function were similar in the SNP-treated and standard PPCI arms.

Diagnostic quality T2-weighted short-tau inversion recovery (T2w-STIR) (oedema) imaging, required for area-at-risk (AAR) estimation and derivation of the myocardial salvage index (MSI), was obtainable in only 109 patients (55%). There was no significant difference in MSI between groups for those in whom oedema assessment was performed.

Echocardiography was performed at 3 months in 108 (44%) subjects ($n = 44$ adenosine group, $n = 30$ SNP group, $n = 34$ control group). The ejection fraction [%, median, interquartile range (IQR)] was significantly higher in the control arm (58.5, 54.5–64.0) than in the adenosine arm (53.5, 41.3–60.0; $p = 0.010$) and SNP arm (51.5, 45.0–61.0; $p = 0.015$).

Patients were followed up for a median of 6 months. In total, 232 patients (94%) completed follow-up (four patients died before follow-up was completed, four patients withdrew consent, five patients refused follow-up and two patients were lost to follow-up). There was a significant increase in MACEs in patients undergoing adenosine-facilitated PPCI compared with control patients, driven by heart failure, at 30 days [hazard ratio (HR) 5.39, 95% CI 1.18 to 24.60; log-rank $p = 0.04$] and 6 months (HR 6.53, 95% CI 1.46 to 29.2; log-rank $p = 0.01$) post randomisation. There was no statistically significant difference in bleeding between groups.

Almost one in five patients randomised to drug-facilitated PPCI did not receive the second dose of study drug post-stent deployment as a result of increased corrected QT interval (QTc) following the first dose (a predefined safety precaution). Consequently, secondary analysis per protocol was performed; patients who received both doses of study drug in the adenosine arm as per protocol had an even stronger statistically significant signal of harm in CMR parameters than patients in the control arm. Infarct size was increased in adenosine-treated patients compared with control patients ($p = 0.031$) and increased LV volumes and reduced ejection fraction were also observed in the adenosine arm. Considering only patients who received both doses of study drug, time to first event analysis again showed a statistically significant increased HR for adenosine-facilitated PPCI compared with the control group at 30 days (HR 5.91, 955 CI 1.28 to 27.25; log-rank $p = 0.036$) and 6 months (HR 7.31, 95% CI 1.62 to 33.0; log-rank $p = 0.008$) post randomisation.

Survival analysis demonstrated a clear signal of increased hazard with adenosine-facilitated PPCI compared with the control. Our clinical outcome data are consistent with the CMR imaging data (increased LV volumes, reduced ejection fraction and increased infarct size), which together suggests possible adverse LV remodelling with adenosine treatment leading to worse clinical outcomes than with standard PPCI (control).

Conclusions

The REFLO-STEMI trial was a well-designed trial that tested two drugs, adenosine and SNP, in appropriate doses and delivered locally, and used a sensitive marker (CMR imaging) of the potential impact of these drugs on flow and therefore infarct size. There was no demonstrated efficacy with either drug. However, an increase in MACEs rate was observed with adenosine, which we believe to be real. Our study suggests that high-dose IC adenosine delivered during PPCI treatment of STEMI may lead to cardiac toxicity and adverse outcome. Accordingly, high-dose IC adenosine should not be used in the setting of PPCI to prevent reperfusion injury.

Trial registration

This trial is registered as ClinicalTrials.gov NCT01747174 and EudraCT 2010–023211–34.

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