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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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Abstract

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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Background: Microvascular obstruction (MVO) predicts short- and longer-term outcomes following primary percutaneous coronary intervention (PPCI) treatment of ST-elevation myocardial infarction (STEMI). The evidence base supporting the role of adenosine and sodium nitroprusside (SNP), the most evaluated adjunctive therapies aimed at attenuating MVO and infarct size, remains weak as the trials involved have had variable end points and used differing drug doses and modes of delivery.

Objective: To determine whether intracoronary administration of adenosine or SNP following thrombus aspiration reduces infarct size and/or MVO measured by cardiac magnetic resonance (CMR) imaging in patients undergoing PPCI within 6 hours of onset of STEMI.

Design: Multicentre, prospective, parallel, randomised controlled and open-label trial with blinded end point analysis.

Setting: Four high-volume UK PPCI centres.

Participants: Patients with STEMI undergoing PPCI with Thrombolysis in Myocardial Infarction (TIMI) flow grade 0/1 in the infarct-related artery and no significant bystander coronary artery disease on angiography.

Interventions: Participants were anticoagulated with bivalirudin and allocated by an automated 24-hour telephone randomisation service to one of three groups: (1) standard PPCI (control), (2) PPCI with adjunctive adenosine 1–2 mg or (3) PPCI with adjunctive SNP 250 µg. The study drugs were delivered intracoronary immediately following thrombus aspiration and again following successful stenting.

Main outcome measures: The primary outcome was infarct size (% total left ventricular end-diastolic mass; %LVM) measured by CMR imaging undertaken 48–96 hours post PPCI. Secondary outcome measures included MVO (hypoenhancement within the infarct core) on CMR imaging, electrocardiographic and angiographic markers of microvascular perfusion and major adverse cardiac events (MACEs) during a median of 6 months' follow-up. The study aimed to recruit 240 patients (powered at 80% to detect a 5% absolute reduction in infarct size).

Results: The trial completed recruitment in April 2014 having randomised 247 patients (standard PPCI group, $n = 86$; PPCI + adenosine group, $n = 82$; PPCI + SNP group, $n = 79$). In total, 79% of participants were male and the mean ± standard deviation age of participants was 59.3 ± 12.3 years. CMR imaging was completed in 197 (80%) patients (standard PPCI, $n = 65$; PPCI + adenosine, $n = 63$; PPCI + SNP, $n = 69$) for the primary outcome. There was no significant difference in infarct size [%LVM, median, interquartile range (IQR)] between the adenosine group (10.1, 4.7–16.2), the SNP group (10.0, 4.2–15.8) and the control group (8.3, 1.9–14.0) ($p = 0.062$ and $p = 0.160$ vs. control, respectively). MVO (%LVM, median, IQR) was similar across the groups [1.0, 0.0–3.7 ($p = 0.205$) and 0.6, 0.0–2.4 ($p = 0.244$) for adenosine and SNP, respectively, vs. 0.3, 0.0–2.8 for the control]. Using per-protocol analysis, infarct size (%LVM) was increased in adenosine-treated patients compared with control patients (12.0 vs. 8.3; $p = 0.031$). Increased left ventricular volume and reduced left ventricular ejection fraction were also observed in the adenosine arm. 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% confidence interval (CI) 1.18 to 24.60; $p = 0.04$] and 6 months (HR 6.53, 95% CI 1.46 to 29.2; $p = 0.01$) post randomisation.

Conclusions: High-dose intracoronary adenosine and SNP during PPCI did not reduce infarct size or MVO measured by CMR imaging. Furthermore, adenosine may adversely affect mid-term clinical outcome and should not be used during PPCI to prevent reperfusion injury.

Trial registration: ClinicalTrials.gov NCT01747174 and EudraCT 2010–023211–34.

Funding: This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a MRC and NIHR partnership.

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AAR	area at risk
ACE	angiotensin-converting enzyme
AMISTAD	Acute Myocardial Infarction STudy of ADenosine
AV	atrioventricular
CI	confidence interval
CK	creatine kinase
CMR	cardiac magnetic resonance
cTFC	corrected TIMI frame count
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
GPIIbIIIa	glycoprotein IIb/IIIa
HR	hazard ratio
IC	intracoronary
IMH	intramyocardial haemorrhage
IQR	interquartile range
IRA	infarct-related artery
ITT	intention to treat
LAX	long axis
LGE	late gadolinium enhancement
LV	left ventricular
LVEF	left ventricular ejection fraction
LVM	total left ventricular end-diastolic mass
MACE	major adverse cardiac event
MBG	myocardial blush grade
MCE	myocardial contrast echocardiography
MI	myocardial infarction
MRC	Medical Research Council
MSI	myocardial salvage index
MVO	microvascular obstruction
NIHR	National Institute for Health Research
NO	nitric oxide
NT-proBNP	N-terminal pro-brain natriuretic peptide
PCI	percutaneous coronary intervention
PPCI	primary percutaneous coronary intervention
PPI	patient and public involvement
QTc	corrected QT interval
QuBE	Quantitative Blush Evaluator
RCA	right coronary artery
SAX	short axis
SD	standard deviation
SNP	sodium nitroprusside
SPECT	sestamibi single-photon emission computed tomography
STEMI	ST-elevation myocardial infarction
STR	ST-segment resolution
T2w	T2-weighted
T2w-STIR	T2-weighted short-tau inversion recovery
TFG	TIMI flow grade
TIMI	Thrombolysis in Myocardial Infarction
TMPG	TIMI myocardial perfusion grade
TSC	Trial Steering Committee

Plain English summary

Heart attacks are often caused by a blood clot in a heart artery obstructing blood flow to heart muscle but, despite removing this blockage, blood flow may not be fully restored because of poor flow in the small distal branches supplying heart muscle. Heart specialists do not currently know how to prevent this, although adenosine and sodium nitroprusside (SNP), two well-studied agents, may improve the blood supply to heart muscle by limiting small vessel obstruction during treatment of a heart attack.

The REperfusion Facilitated by LOcal adjunctive therapy in ST-Elevation Myocardial Infarction (REFLO-STEMI) study randomly allocated 247 patients presenting within 6 hours of a heart attack to (1) standard angioplasty (control group), (2) standard therapy plus adenosine or (3) standard therapy plus SNP. The effectiveness of the drugs was assessed using magnetic resonance imaging (MRI), which can accurately quantify the amount of small vessel obstruction and heart muscle damage that will ultimately form scar tissue. The degree of heart muscle damage and obstruction to blood flow on MRI are strongly related to subsequent complications following a heart attack.

We found that the study drugs did not reduce either the amount of heart muscle damaged or the extent of small vessel obstruction following a heart attack. There may even be a small increase in heart muscle injury and a higher risk of heart failure during follow-up associated with high-dose adenosine given during the treatment of a heart attack. Our study, therefore, discourages the use of high doses of adenosine to prevent heart muscle injury.

Scientific summary

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.

Funding

This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a MRC and NIHR partnership.

Chapter 1 Introduction

Ischaemic heart disease is a leading cause of morbidity and mortality worldwide, with more than 100,000 patients presenting with ST-elevation myocardial infarction (STEMI) in the UK each year.[1] Timely delivered primary percutaneous coronary intervention (PPCI) has become the primary reperfusion therapy for STEMI in the USA and Europe.[2] However, this interventional technique has not abolished the unpredictable phenomenon of no-reflow and the underappreciated, but potentially equally important, syndrome of abnormal epicardial-microvascular obstruction (MVO).

Microvascular obstruction describes abnormal tissue perfusion and/or coronary blood flow despite normal patency of the infarct-related artery (IRA).[3] This can result in persistent myocardial injury and necrosis through interacting processes. Distal microembolisation of thrombus and plaque debris, activation of the inflammatory cascade, neutrophil plugging, toxic free-radical generation and capillary obstruction by intraluminal (endothelial protrusion by cell swelling and cellular infiltrate rich in red blood cells, platelets and granulocytes) and extraluminal (compression from surrounding oedematous myocytes) mechanisms promote poor perfusion and irreversible injury to potentially viable myocytes.[3–10] These ultrastructural and functional changes result in a spectrum of MVO that, as detected by cardiac magnetic resonance (CMR) imaging, manifests in up to 70% of patients with STEMI treated with PPCI.[11–17] Although the incidence of MVO varies between studies, presumably because of a combination of modifiable and non-modifiable patient-related factors, its presence been reported to be associated with major adverse cardiac event (MACE) rates of up to 30% at 1 month and 60% at 12 months.[12]

Manual thrombectomy has been shown to improve angiographic microvascular flow irrespective of the presence of visible thrombus[18] and to reduce infarct size and preserve microvascular integrity assessed by CMR imaging,[19] leading to improved left ventricular (LV) function and tissue perfusion assessed by myocardial contrast echocardiography (MCE).[20] However, there is conflicting evidence whether this leads to overall improved clinical outcomes, although the large ongoing TOTAL trial [randomized trial of routine aspiration ThrOmbecTomy with percutaneous coronary intervention (PCI) versus PCI ALone in patients with ST-elevation myocardial infarction undergoing primary PCI] will provide further insights.[21–27] Glycoprotein IIb/IIIa (GPIIbIIIa) inhibitors further reduce infarct size and improve markers of microvascular perfusion in STEMI patients undergoing PPCI.[28–30] Bivalirudin has been shown in the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY)[31] and HORIZONS-AMI (Harmonizing Outcomes with RevascularIZatiON and Stents in Acute Myocardial Infarction)[32] trials to provide similar efficacy with less bleeding and even reduced mortality compared with unfractionated heparin plus GPIIbIIIa receptor inhibitors in high-risk patients undergoing PPCI. However, residual mortality and subsequent MACE rates suggest that there is room for improvement even in those patients who do not demonstrate slow-flow or no-reflow angiographically.

Basic understanding of the MVO process has led to the evolution of several treatment regimens designed to improve outcome, including the use of vasodilators,[33–41] albeit mostly in clinical trials. Of these, sodium nitroprusside (SNP)[13,42–49] and adenosine[44,50–62] and their effects on attenuating or preventing MVO have been the most studied. The randomised controlled trials of adenosine and SNP in PPCI are presented in *Appendix 1*. Adenosine, aside from being a potent vasodilator,[63] may have additional benefits because of its pleiotropic effects: the anti-inflammatory action of adenosine is well recognised[64,65] and its ability to block the neutrophil-mediated processes that promote MVO may explain the reduction in reperfusion injury seen with intracoronary (IC) adenosine in canine infarct models.[66] Similarly, SNP, a direct nitric oxide (NO) donor that requires no intracellular metabolism,[67] utilises NO's multiple vascular functions. These include vasodilatation of arterioles, inhibition of platelet adhesion and anti-inflammatory activity,[68] which effectively reduce no-reflow in animal reperfusion injury models.[69,70] SNP and adenosine have, in some trials, demonstrated a favourable improvement in electrocardiographic and angiographic markers of microvascular perfusion, as well as improvements in short-term MACE rates.[42,44,55,71] The randomised and placebo-controlled Acute Myocardial Infarction STudy of ADenosine (AMISTAD)-II trial sought to determine the benefits of adenosine in 2118 patients presenting within 12 hours of onset of anterior STEMI treated

with thrombolysis (60%) or PPCI (40%).[59] Infarct size and adverse clinical events were reduced in a subgroup who received a higher (70 µg/kg/minute) dose of adenosine and in those reperfused within 3 hours of symptom onset. This trial, although the largest to date, has a number of limitations in addition to the mixed reperfusion strategy cohort: (1) adenosine was administered by intravenous infusion *after* the PPCI, (2) infarct size was measured relatively late after presentation in only 11% of patients and by technetium-99m sestamibi single-photon emission computed tomography (SPECT), which may underestimate infarct size compared with CMR imaging, and (3) no measure of myocardial salvage was obtained. Overall, the AMISTAD-II study appears not to be applicable in the modern PPCI era.

The effects of adenosine on the coronary microcirculation during STEMI have been assessed using CMR imaging in only one previous study. Desmet *et al.*[51] assessed whether IC administration of adenosine, distal to the occlusion site and immediately before initial balloon inflation, resulted in increased myocardial salvage and decreased MVO compared with placebo on CMR imaging at 48–72 hours post PPCI in 112 patients. They reported no significant difference in myocardial salvage between the two groups (41.3% vs. 47.8%; $p = 0.52$). MVO extent, angiographic markers of reperfusion and infarct size at 4 months were also similar in both groups. Interestingly, the authors reported a statistically significant benefit in favour of adenosine in patients with Thrombolysis in Myocardial Infarction (TIMI) flow grade (TFG) 2–3 pre PPCI. This suggested that establishing flow prior to adenosine delivery was beneficial and perhaps necessary for the drug to have a clinical effect. As thrombectomy was not performed in this study, it is possible that adenosine may have been ineffective because of a combination of its short half-life and failure to reach the distal vascular bed. In addition, more patients had an anterior myocardial infarction (MI) in the adenosine group (48% vs. 33%). Anterior STEMI is known to be associated with larger infarct sizes, reduced myocardial salvage and increased LV remodelling.[72] Moreover, the spontaneous reperfusion rate was high (28%) in this study, evident as TFG 2–3 prior to PPCI. The placebo group had almost twice as many patients with established TFG 2–3 prior to PPCI and this is known to be associated with higher myocardial salvage and reduced infarct size. Finally, the expression of MVO indexed to the area at risk (AAR) rather than infarct size or total LV mass has not been described previously in the evidence base and is unexplained in this study.

Although benefits have been shown for both adenosine and SNP in smaller trials, the results of such studies have been largely conflicting and hence there is currently no consensus on the value of routine administration of adjunctive pharmacotherapeutic agents to prevent or reduce MVO. In fact, a recent Cochrane review[73] found that adenosine, when given as an adjunct during PPCI, did not reduce all-cause mortality, non-fatal MI or the incidence of angiographic no-reflow. However, the authors conceded that the evidence base was limited and highlighted the need for further research with larger high-quality trials. Heterogeneity in trial design (small numbers of participants, suboptimal drug dosages, inadequate antiplatelet therapy and variably chosen end points often lacking imaging confirmation of MVO and infarct size) has resulted in contradictory outcome data that may not be clinically applicable. Consequently, there is divergent clinical practice, even within institutions. Furthermore, the incidence of no-reflow/MVO remains difficult to predict on coronary angiography alone. It could be argued that, given the strong relationship between MVO and prognosis, prophylactic prevention of MVO should be considered in all patients presenting with STEMI, irrespective of the thrombus burden, with delivery of agents theoretically able to reduce MVO.

The failure of some previous randomised clinical trials to show a reduction in MVO may in part be related to factors other than clinical efficacy. The lack of a sensitive imaging modality to detect MVO and the failure to deliver vasoactive agents close to the microvascular bed may potentially have reduced their therapeutic impact.

We therefore designed the REperfusion Facilitated by LOcal adjunctive therapy in ST-Elevation Myocardial Infarction (REFLO-STEMI) study to evaluate whether adjunctive adenosine or SNP, administered in two doses (the first optimally delivered by distal IC injection following thrombectomy), would be effective in preventing MVO and reducing infarct size, as determined using the sensitive measure of CMR imaging, in patients undergoing PPCI for STEMI.[74]

Chapter 2 Research objectives

The original research objective of the REFLO-STEMI trial was to determine whether IC adenosine and/or SNP reduces CMR-measured infarct size (% total left ventricular end-diastolic mass; %LVM) at 48–72 hours post PPCI.

Secondary questions were as follows.

1. What is the expected size of effect of both SNP and adenosine on MVO (incidence and absolute reduction in MVO as %LVM)?
2. What is the CMR incidence and extent of MVO (%LVM) at 48–72 hours post PPCI?
3. What is the impact of the study drugs on the CMR-measured myocardial salvage index (MSI), haemorrhage, left ventricular ejection fraction (LVEF) and volumes in the acute stage?
4. Does administration of IC adenosine and/or SNP reduce angiographic markers of MVO?
5. What is the incidence of angiographic slow-flow/no-reflow after PPCI with the three different management strategies?
6. Is there a difference in the incidence of complete (> 70%), and degree of, ST-segment resolution (STR) between the three treatment arms?
7. Do the study agents affect overall MACE rates and their components at 6 months, namely death, need for target lesion revascularisation, recurrent MI, severe heart failure and cerebrovascular event?

Chapter 3 Methods

Study design

The REFLO-STEMI trial was a multicentre randomised controlled open-label clinical trial undertaken in four regional cardiac centres in the UK. All patients presenting within 6 hours of symptom onset of STEMI, who were suitable for reperfusion by PPCI and had a baseline corrected QT interval (QTc) of < 450 milliseconds on admission electrocardiography (to limit the risk from the possible QT prolongation effect of the study drugs), were provisionally eligible to participate in the study. TFG 0–1 in the IRA and no flow-limiting bystander disease (i.e. no stenosis ≥ 70% in non-IRAs) were prerequisites for randomisation. Full eligibility criteria are provided in *Table 1*. Following verbal consent (also referred to as assent[75,76]), patients were randomised 1 : 1 : 1 to adjunctive IC adenosine, SNP or control (standard PPCI alone) by a member of the research team using a dedicated 24/7 computerised telephone service (provided by the Sealed Envelope Ltd, London, UK) with stratification by (1) symptoms to balloon of < 3 hours or ≥ 3 hours and (2) anterior infarction or not.

In all cases PPCI was performed in line with accepted practice with transradial or femoral arterial access using 6 and 7 Fr sheaths. Patients were pretreated with dual antiplatelet therapy with aspirin (300-mg loading dose and 75 mg/day maintenance dose) and prasugrel (60-mg loading dose and 10 mg/day maintenance dose)[77,78] or ticagrelor (180-mg loading dose and maintenance dose of 90 mg twice daily), given for up to 12 months.[79–81] Bivalirudin was administered to all patients (0.75-mg/kg bolus plus infusion of 1.75 mg/kg/hour) [as was standard practice then, i.e. prior to the HEAT-PPCI (How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) trial[82]] in the absence of specific contraindication, with dose reduction for renal insufficiency, and was discontinued at the completion of PPCI (but could have been continued for 4 hours if clinically indicated). For patients randomised to an intervention arm, following manual thrombectomy and thorough flushing of the catheter the first drug dose (adenosine 1 mg or SNP 250 µg) was injected as distally as possible via the thrombus aspiration catheter. Immediately following stent deployment, and providing a repeat measure of QTc was < 450 milliseconds and remained < 60 milliseconds above the baseline value, the second drug dose (1 mg of adenosine if the IRA was the right coronary artery (RCA); otherwise, 2 mg of adenosine or 250 µg of SNP) was given by slow injection (> 1 minute) via the guide catheter. Administering the second drug dose distal to the stent via the thrombectomy catheter had been considered in the trial planning phase but the risk associated with crossing the stent with the thrombectomy catheter was thought to outweigh the benefit of distal drug delivery.

TABLE 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
• ≥ 18 years of age • Informed assent (verbal consent) prior to angiography • STEMI presenting within 6 hours of symptom onset requiring PPCI • Single-vessel coronary artery disease (non-culprit disease < 70% stenosis at angiography) • TIMI flow 0/1 at angiography • QTc < 450 milliseconds	• Contraindications to PPCI, CMR imaging, contrast agents or study medications • SBP ≤ 90 mmHg • Cardiogenic shock • Previous Q-wave MI • Culprit lesion not identified or located in a bypass graft • Stent thrombosis • Left main disease • Known severe asthma • Known stage 4 or 5 chronic kidney disease (eGFR < 30 ml/minute/1.73 m^2) • Pregnancy

eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

The electrocardiogram (ECG) was recorded and retained at each angiography time point. The degree of STR was determined from 12-lead ECGs acquired pre and post PPCI and categorised as complete (> 70%), partial (30–70%) or no (< 30%) STR.[17,83] The maximal sum of ST-segment elevation, measured 60 milliseconds after the J point, was calculated from three contiguous leads in the infarct territory.

Angiographic images were acquired at 30 frames per second with long acquisitions (to visualise the venous phase in contrast passage) in orthogonal views before intervention and after stenting (at the time of the final/optimal angiographic result) to enable determination of angiographic markers of MVO offline at a core laboratory (Newcastle University); TIMI myocardial perfusion grade (TMPG) was assessed visually as previously described[84,85] (*Table 2*). Digital quantification of myocardial perfusion or 'blush' was performed using QuBE (Quantitative Blush Evaluator) version 1.0 software (University of Groningen, the Netherlands);[86] corrected TIMI frame count (cTFC) was calculated as the number of cine frames needed for the dye to reach standardised distal landmarks, to objectively evaluate coronary blood flow as a continuous variable.[87,88] The final TFG < 3 (*Table 3*) was also taken to represent angiographic MVO post PPCI.[89] Thrombus score was reported according to TIMI criteria (*Table 4*).[90] A list of angiographic markers of MVO assessed is provided in *Table 5*.

TABLE 2 Thrombolysis in myocardial infarction myocardial perfusion grade[84]

TMPG	Definition
0	Failure of dye to enter the microvasculature
1	Dye slowly enters but fails to exit the microvasculature
2	Delayed entry and exit of dye from the microvasculature
3	Normal entry and exit of dye from the microvasculature

TABLE 3 Thrombolysis in myocardial infarction flow grade classification[89]

TFG	Definition
0	No perfusion
1	Penetration without perfusion
2	Partial perfusion
3	Complete perfusion

TABLE 4 Thrombolysis in myocardial infarction thrombus score[90]

TIMI thrombus score	Definition
0	No characteristics of thrombus
1	Possible thrombus, as reduced contrast density, haziness, irregular lesion contour or a smooth convex 'meniscus' at the site of total occlusion suggestive but not diagnostic of thrombus
2	Definite thrombus, with greatest dimensions less than half vessel diameter
3	Definite thrombus, greatest linear dimension greater than half but less than two vessel diameters
4	Definite thrombus, largest dimension greater than two vessel diameters
5	Total occlusion

TABLE 5 Study outcome measures

Type of outcome measure	Outcome measure
CMR imaging parameters	• CMR-measured infarct size (%LVM) (primary outcome) • Incidence and extent of MVO (%LVM) • MSI • Intramyocardial haemorrhage • LVEF and LV volumes
Angiographic markers of MVO	• TFG[89] • cTFC[87,88] • TMPG[84,85,91] • Computer-assisted myocardial blush quantification using QuBE software[86] • Incidence of angiographic slow-flow/no-reflow after PPCI
Electrocardiography	• Degree of STR on electrocardiography[17,83]
Echocardiography	• LV function at baseline and 3 months
Subanalyses	• Overall MACE rate and its components at 1 month: death, need for TLR, recurrent MI, severe heart failure and CVE

CVE, cerebrovascular event; TLR, target lesion revascularisation.

Following the PPCI procedure, and when clinically stable, patients were provided with a detailed patient information leaflet and were then asked for written informed consent to continue participation in the trial. A 20% dropout rate (high allowance because of the CMR imaging component) between PPCI and CMR imaging was allowed for. Studies on informed consent in acute MI patients have suggested that oral information is far better received, processed and recalled by patients than written information.[92,93] In the ISIS-4 (Fourth International Study of Infarct Survival) patient cohort, 95% of participants recalled receiving the oral information whereas only 37% recalled receiving the written consent form.[92] Furthermore, only 18% of 346 patients prospectively studied reported reading the patient information sheet before providing or refusing consent to participate in the Hirulog and Early Reperfusion or Occlusion (HERO)-2 acute MI trial.[93] Of particular note is that patients who gave consent were more likely to report good or partial understanding of the written material than those who refused consent. This raises the possibility of selection bias at the time of consent. Consequently, we believe that verbal explanation of a trial may be a more effective and valuable source of information than a written consent form in the emergent situation of STEMI, when treatment must be provided without undue delay. This approach has also been successfully used in two recent STEMI trials.[75,76]

Blood samples were drawn at baseline and at 4, 12 and 24 hours after PPCI for cardiac enzyme [creatine kinase MB isoenzyme (CK-MB) and troponin] estimation and pre discharge for N-terminal pro-brain natriuretic peptide (NT-proBNP) estimation. Electrocardiographic recording was undertaken at 90 minutes, 24 hours and pre discharge. All patients were commenced on a beta-blocker, angiotensin-converting enzyme (ACE) inhibitor and high-dose statin in addition to dual antiplatelet therapy, unless contraindicated, according to international guidelines.[1]

Patients underwent CMR imaging at 48–72 hours after presentation with STEMI on a 3.0-T scanner with retrospective electrocardiographic gating and dedicated cardiac receiver coils at each of the four participating centres (*Figure 1*) to provide the primary end point.[94,95] Prior to contrast administration, T2-weighted short-tau inversion recovery (T2w-STIR) imaging with coil signal intensity correction was performed in long-axis (LAX) views and contiguous short-axis (SAX) slices covering the entire left ventricle to assess for oedema (AAR). Three SAX (base, mid and apical) tagged images were acquired using a prospectively gated spatial modulation of magnetisation (SPAMM) gradient-echo sequence. Early gadolinium enhancement (EGE) imaging was acquired 1–3 minutes after administration of 0.15 mmol/kg of gadolinium-DTPA (diethylenetriamine penta-acetic acid) (Magnevist®; Bayer) using a single-shot inversion-recovery gradient-echo sequence. Functional assessment of LVEF and LV volumes and mass was according to current standards with the use of a steady-state

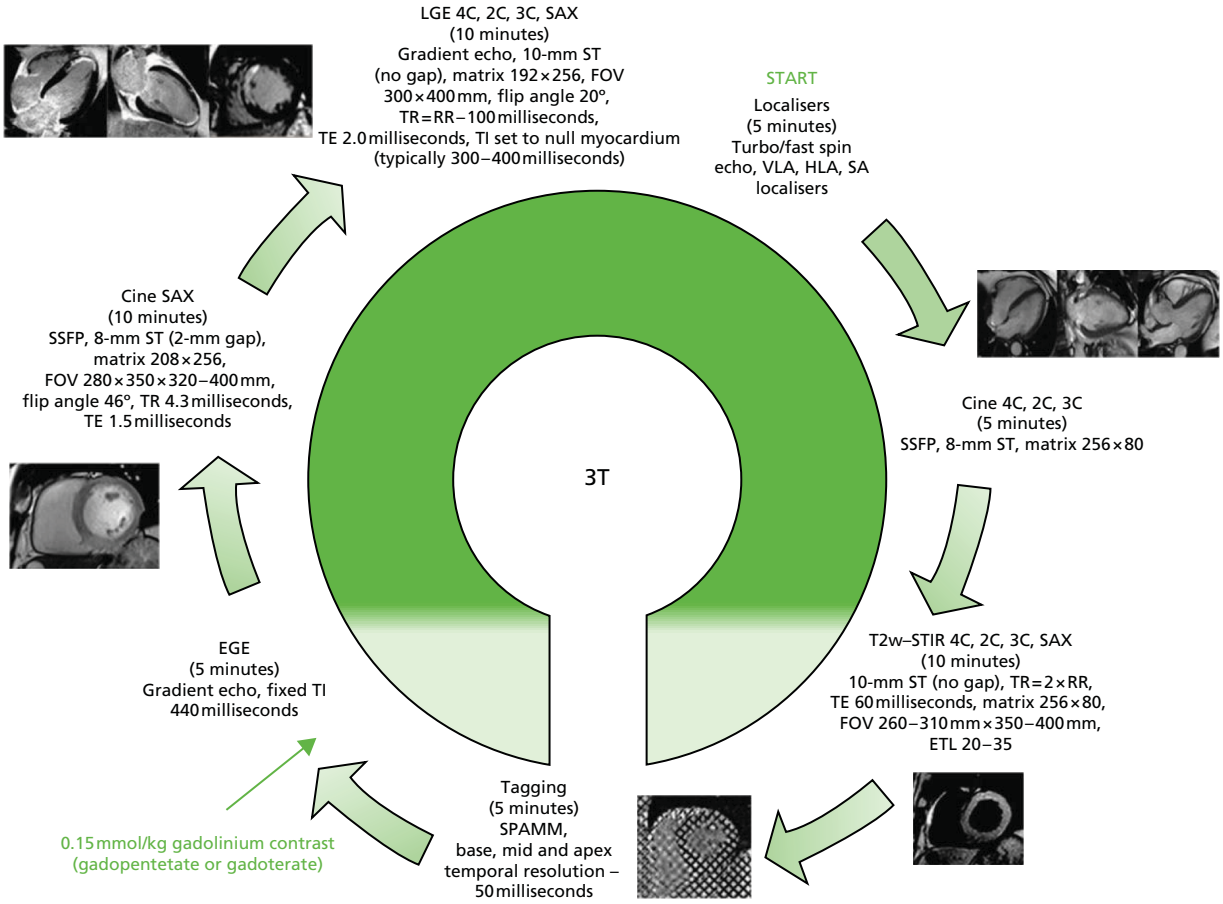

FIGURE 1 Cardiac magnetic resonance imaging protocol. 2C, 3C, 4C, two-, three- and four-chamber LAX views. EGE, early gadolinium enhancement; ETL, echo train length; FOV, field of view; HLA, horizontal long axis; RR, ECG RR interval; SA, short axis; SPAM, spatial modulation of magnetisation; SSFP, steady-state free precession; ST, slice thickness; TE, echo time; TI, inversion time; TR, repetition time; VLA, vertical long axis.

free precession (SSFP) cine pulse sequence covering the whole left ventricle with 8–12 contiguous SAX slices. Late gadolinium enhancement (LGE) imaging[96] was then performed in LAX (two-/three-/four-chamber) views and contiguous SAX slices covering the whole left ventricle. LGE images were acquired 10–15 minutes post contrast using a segmented inversion-recovery gradient-echo sequence. The inversion time was progressively adjusted to null unaffected myocardium. The full study outcome measures are listed in *Table 5*.

Cardiac magnetic resonance analysis, blinded to patient details, was undertaken in a central core lab (University of Leicester) using cmr[42] software (Circle Cardiovascular Imaging, Calgary, AB, Canada). Anonymised CMR images were graded for image quality before analysis using a 4-point scale (4 = excellent, 3 = good, 2 = moderate and 1 = non-analysable). Endocardial and epicardial borders were manually contoured on contiguous SAX LV slices, excluding papillary muscles, trabeculae and blood-pool artefact, for LV volumetric, AAR and infarct size analyses. Infarct was identified as enhancement on LGE images and quantified using the full-width half-maximum (FWHM) technique.[97] MVO was defined (and quantified) as hypoenhancement within infarcted myocardium, as determined from LGE images, and was included in the total infarct size. Myocardial oedema was quantified using semi-automatic thresholding, defining AAR as enhancement within myocardium of signal intensity > 2 standard deviations (SDs) above that of a region of interest contoured in remote myocardium. Hypoenhanced areas within the AAR were regarded as intramyocardial haemorrhage (IMH). The MSI was calculated as 100 × [(AAR – infarct size)/AAR]. Infarct size, MVO, AAR and IMH were expressed as %LVM and LV volumes were indexed to body surface area. Intra- and interobserver variability is reported for the primary outcome measure. The tagging data will be analysed as a separate substudy and presented in a separate publication.

All patients were followed up for at least 1 month following randomisation and throughout the course of the study until the last patient recruited to the trial had completed the 1-month follow-up. Median follow-up is reported. Patients were also flagged with the Office for National Statistics to ensure capture of mortality data. Most adverse events were expected as recognised complications of STEMI or the revascularisation procedure. Such events were recorded for the evaluation of outcome measures and for safety monitoring. Definitions of important adverse events are provided in *Table 6*. Investigators were required to notify the co-ordinating centre (University Hospitals of Leicester NHS Trust, UK) within 24 hours if any of the following adverse events occurred: death; a serious deterioration in a patient's health that resulted in a life-threatening injury or illness; an event resulting in permanent impairment of a body structure or function; an event resulting in medical or surgical intervention to prevent permanent impairment to a body structure or function; or an event prolonging inpatient hospitalisation. On receipt of notification of any trial adverse or clinical event, the co-ordinating centre requested additional details specific to the nature of the event and carefully monitored the episode. A clinical events committee was established to review and adjudicate key trial adverse events, blinded to patient details and treatment allocation, using original source documents.

Statistical methods

Demographics are presented and values of infarct size and MVO are summarised, both overall and by treatment group. The distribution of continuous variables, including infarct size, was investigated and when found to be non-normally distributed was log-transformed prior to analysis. Normally distributed continuous variables were expressed as mean ± SD and compared using linear mixed models.

TABLE 6 Definitions of adverse events

Adverse event	Definition
Cardiogenic shock	Systolic blood pressure < 90 mmHg for at least 30 minutes (or the need for supportive measures to maintain a systolic blood pressure of > 90 mmHg) in the presence of a heart rate of > 60 beats/minute in association with signs of end-organ hypoperfusion (cold extremities, low urinary output of < 30 ml/hour and/or mental confusion)
MI	MI was defined differently in specific clinical situations in this trial. The European Society of Cardiology (ESC) and American College of Cardiology (ACC) criteria for acute, evolving or recent MI were applied[98]
Reinfarction	Further chest pain during the index admission lasting > 20 minutes accompanied by new electrocardiographic changes (new Q waves > 0.04 seconds or ST-segment elevation > 0.1 mV in two leads for > 30 minutes), further enzyme rise or both
Recurrent MI	A ≥ 20% rise in the value of the biomarker measured serially 6–12 hours apart, provided the absolute value was greater than the 99th percentile upper reference limit. For patients who died and for whom no cardiac markers were obtained, the presence of new ST-segment elevation and new chest pain would meet criteria for MI
Contrast-induced nephropathy	A 25% increase in serum creatinine concentration from the baseline value or an absolute increase of at least 0.5 mg/dl (44.2 µmol/l), appearing within 48 hours of administration of contrast media and maintained for 2–5 days[99–101]
Cerebrovascular events	Stroke was defined as a new focal neurological deficit of presumed vascular aetiology persisting for > 24 hours combined with a neurological imaging study that did not indicate a different aetiology. Transient ischaemic attack was any focal ischaemic neurological deficit of abrupt onset, which resolved completely within 24 hours
Severe heart failure	*Early* heart failure: any new-onset cardiogenic shock or heart failure occurring after randomisation and during the index admission with radiographic evidence of pulmonary oedema requiring intravenous diuretic therapy. *Late* heart failure: admission to hospital for treatment for documented New York Heart Association (NYHA) class III or IV heart failure
Major bleeding	Defined according to the TIMI criteria as fatal bleeding, any intracranial bleeding or clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥ 50 g/l

Non-normally distributed data were presented as median (25th–75th quartiles) and compared using non-parametric methods such as the Mann–Whitney or the Kruskal–Wallis test.

Primary analysis was by intention to treat (ITT) with a secondary analysis by treatment received, that is, per protocol. Patients entering into the study but not completing the CMR imaging continued to be followed up for MACEs on an ITT basis. For continuous outcomes, including infarct size, *t*-tests were used to compare means between groups; comparison between the groups for categorical outcomes was undertaken using chi-squared tests. Each drug was compared with the control (i.e. adenosine vs. control and SNP vs. control). Multivariable analysis using linear regression took into consideration possible confounders such as sex, age and other comorbidities. The major confounders of location of infarct (anterior/non-anterior) and time from symptom onset to reperfusion were addressed by the stratified randomisation process. Other important confounders, such as collateral blood flow to the infarct territory determined by the Rentrop score,[98] were assessed in the statistical analysis using a forward selection procedure using a statistical significance level of 5%.

Secondary end point analysis employed time-to-event Cox proportional hazards regression models to investigate potentially important predictors of first MACE (both at 30 days and at the end of the study) and obtain unadjusted and adjusted hazard ratios (HRs) together with 95% confidence intervals (CIs) for adenosine compared with control and SNP compared with control. Further analyses investigating the incremental benefit of infarct size in predicting first MACE at 30 days used Cox proportional hazards regression models to derive a linear predictor, which was then summarised using a receiver operating characteristic curve together with the area under the curve and 95% CI.

Sample size

Sample size was based on previous observations of a significant correlation between the extent of CMR-measured MVO and infarct size (which on average is 20% of LVM as detected by CMR imaging after PPCI).[17] As there were no available data regarding the incidence of MVO with the study drugs assessed by CMR imaging, and because of the wealth of published data on infarct size following PPCI, we chose infarct size as the primary end point of the trial. Infarct size is a powerful predictor of ventricular function, adverse LV remodelling and short- to medium-term clinical outcome.[14,16,17,102–114] Furthermore, new infarct size of 4% of LVM has been shown to be associated with adverse prognosis in patients with coronary artery disease undergoing revascularization-related injury.[115] To detect a reduction in infarct size from 20% to 15% of LVM, assuming a SD of 10%,[19,105,111,112,116–120] α of 0.05, two-tailed, 80% power and a drop-out rate of 20% between PPCI and CMR, 80 subjects per group (240 in total) were required. It should be noted that the original sample size was set at 297 patients (99 in each group) based on 90% power. There were many challenges during the recruitment phase, which was difficult for this study. Consequently, we approached the funding body for an extension to the trial with an associated request for additional funding. Unfortunately the request was denied and, hence, to deliver a meaningful trial, the power and sample size of the study were reduced. However, our statistician, and the National Institute for Health Research (NIHR) study progress review body, felt that the reduction in power from 90% to 80% would not affect the final results.

Patient and public involvement

As this grant application went through a fast-track application there was limited time to involve service users. However, the study was presented to the patient and public involvement (PPI) group of the NIHR Leicester Cardiovascular Biomedical Research Unit and was welcomed. A layperson from the public volunteered to join the Trial Steering Committee (TSC) and regularly attended meetings. Co-investigators spoke at regional PPI meetings about active CMR studies and heart disease, including the REFLO-STEMI trial.

Patients who were recruited to the study were given the opportunity to have a one-to-one meeting following their CMR imaging to discuss their CMR and angiographic images. They also had the opportunity to ask any questions that they had in a relaxed atmosphere, which was well received and appreciated.

Once the study results have been published the study will be presented at our local and regional PPI meetings to help disseminate the findings.

Study organisation

This project was funded by the Medical Research Council (MRC) through the Efficacy and Mechanism Evaluation (EME) Board (project number 09/150/28) and managed by the NIHR on behalf of the MRC–NIHR partnership. The trial sponsor was the University Hospitals of Leicester NHS Trust. Trial support was provided by the Leicester Clinical Trials Unit [UK Clinical Research Collaboration (UKCRC) ID 43], which was responsible for database provision, data management and statistical analysis. The study was overseen by a TSC, with an independent chairperson and two additional independent members. Safety data (particularly unexpected adverse events and protocol violations) were scrutinised by an independent Data and Safety Monitoring Board (DSMB), who reported back to the TSC. The DSMB assessed whether adverse events were complications of study treatments or expected consequences of having a STEMI. The DSMB had the remit to terminate the study early in the presence of trial safety concerns; members convened when 115 patients had been recruited and at the end of recruitment. The DSMB remained satisfied that the study was conducted appropriately and found no cause for concern regarding safety.

Chapter 4 Results

Recruitment

The REFLO-STEMI trial began recruitment on 25 October 2011. In total, 247 patients were randomised (last patient recruited on 8 April 2014). The study completed at the end of June 2014 (*Figure 2*). A total of 222 patients (89.9%) consented to CMR imaging post PPCI, although only 207 patients (83.8%) had CMR imaging attempted, with further attrition during the scan (because of claustrophobia or musculoskeletal discomfort) resulting in 197 patients (79.8%) completing CMR imaging for the primary outcome measure of CMR-derived infarct size.

Interim analysis

An interim analysis of the CMR imaging data after 50 patients had been recruited was intended at the outset. However, this could not be undertaken because, for various logistical reasons, the clinical fellow responsible for the day-to-day running of the trial was not in place when recruitment began and then had to be trained to an appropriate standard of practice. The recruitment phase of the study had progressed considerably and hence it was no longer appropriate to perform an interim analysis of the CMR imaging data. An interim safety analysis evaluating adverse events was performed and submitted to the DSMB during this period.

Baseline characteristics

Baseline characteristics for randomised patients and those completing CMR imaging by treatment allocation are presented in *Table 7*. There were no differences in characteristics between those who were randomised and those who completed the CMR imaging. Groups were generally well matched. A reduced incidence of hypercholesterolaemia and statin use was observed in the control group (standard PPCI without adjunctive pharmacotherapy). 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) and the remaining baseline characteristics, with no other statistically significant differences between the groups.

Angiography and primary percutaneous coronary intervention details

A high use of radial vascular access is noted in this contemporary PPCI study (*Table 8*). Thrombectomy was mandated as a precursor to drug delivery and the slightly lower thrombectomy use observed in the control arm was not statistically significant. Drug-eluting stent use was uniformly high across groups, in keeping with a contemporary study. The median length of stented segment was similar in all groups and ranged from 23 to 26 mm.

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 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.

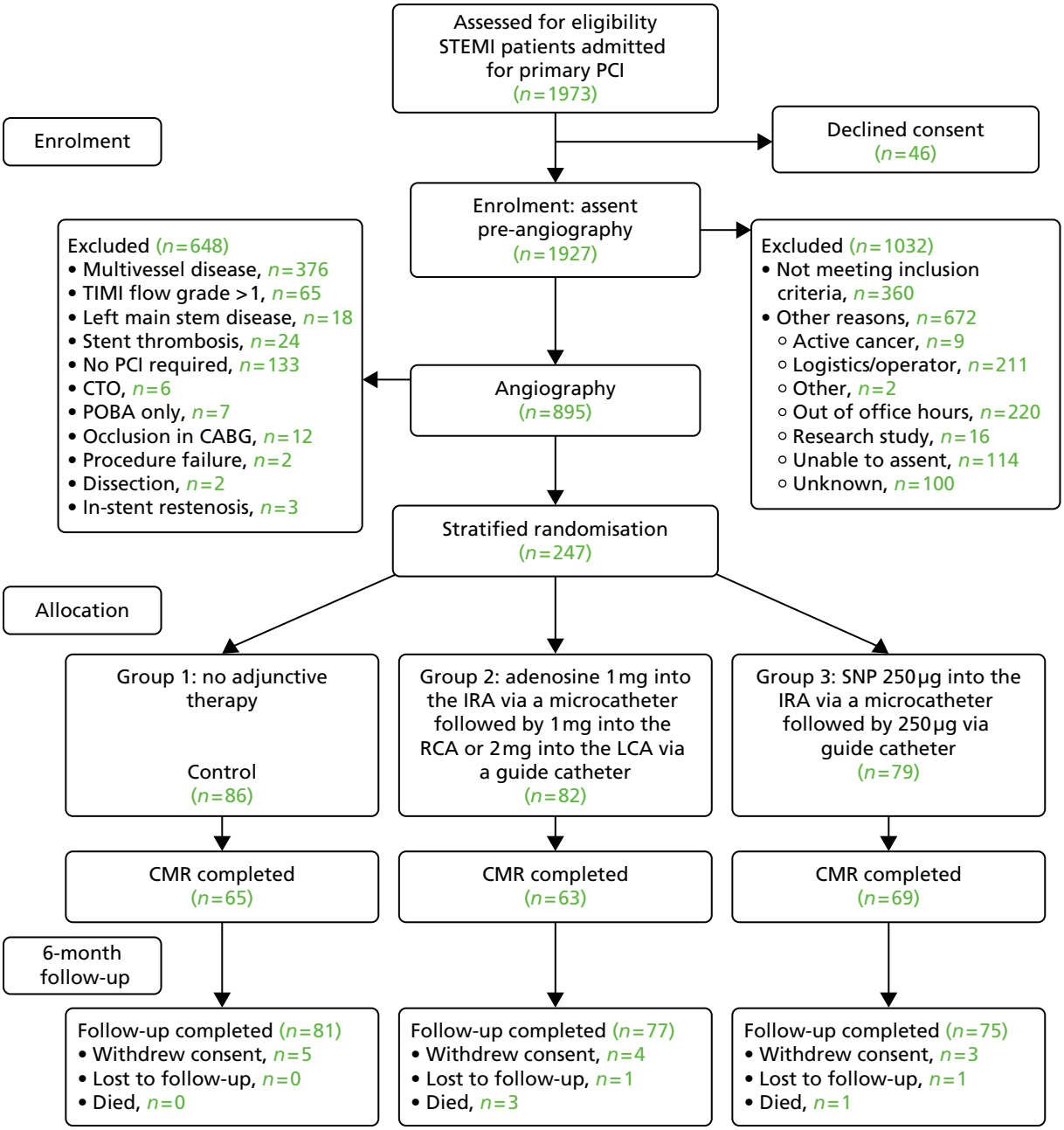

FIGURE 2 Study recruitment flow chart. CABG, coronary artery bypass graft; CTO, chronic total occlusion; LCA, left coronary artery; POBA, plain old balloon angioplasty. Patients who died during the follow-up period were deemed to have completed follow-up and hence, 'Follow-up completed' includes deaths.

Angiographic, electrocardiographic and enzymatic assessment of myocardial injury

The incidence of angiographic slow-flow/no-reflow (TFG < 3 or final visual TMPG 0–1) was low and similar across the groups and was consistent with the quantitative angiographic [myocardial blush grade (MBG) and cTFC] and electrocardiographic (STR > 70%) assessment of microvascular tissue perfusion (*Table 9*). There were no statistically significant differences between these markers of MVO post PPCI.

There was no statistically significant difference in enzymatic infarct size represented by peak creatine kinase (CK) between the groups.

TABLE 7 Demography of the total trial population and the CMR treatment groups[a]

Characteristics	Adenosine		SNP		Control		*p*-value	
	All ($n = 82$)	With CMR data ($n = 63$)	All ($n = 79$)	With CMR data ($n = 69$)	All ($n = 86$)	With CMR data ($n = 65$)	All	With CMR data
Clinical								
Age (years)	57.9 ± 12.8	56.4 ± 12.3	60.5 ± 13.0	59.3 ± 12.5	59.5 ± 11.2	60.0 ± 10.8	0.406	0.192
Male	65/82 (79.3)	52/63 (82.5)	66/79 (83.5)	59/69 (85.5)	64/86 (74.4)	50/65 (76.9)	0.355	0.429
Hypertension	23/82 (28.0)	14/63 (22.2)	26/79 (32.9)	23/69 (33.3)	22/86 (25.6)	16/65 (24.6)	0.574	0.313
Current smoking	47/82 (57.3)	39/63 (61.9)	41/79 (51.9)	37/69 (53.6)	45/86 (52.3)	31/65 (47.7)	0.332	0.238
Diabetes	6/82 (7.3)	3/63 (4.8)	12/79 (15.2)	10/69 (14.5)	9/86 (10.5)	4/65 (6.2)	0.274	0.095
Hypercholesterolaemia	17/82 (20.7)	15/63 (23.8)	23/79 (29.1)	17/69 (24.6)	11/86 (12.8)	6/65 (9.2)	0.035	0.042
Previous MI	0/81 (0)	0/63 (0)	3/79 (3.8)	3/69 (4.3)	3/86 (3.5)	2/65 (3.1)	0.219	0.268
Previous PCI	0/82 (0)	0/63 (0)	3/79 (3.8)	3/69 (4.3)	2/86 (2.3)	1/65 (1.5)	0.225	0.197
Killip class > 1	3/82 (3.7)	2/63 (3.2)	4/79 (5.1)	3/69 (4.3)	4/86 (4.7)	3/65 (4.6)	0.905	0.908
Total ischaemia time (minutes)	159 (124–221)	155 (121–221)	150 (122–201)	150 (121–205)	145 (105–196)	141 (106–188)	0.169	0.209
BMI (kg/m^2)	27.5 (25.0–30.1)	27.5 (25.1–32.1)	26.1 (24.3–30.8)	26.8 (24.7–31.0)	27.3 (24.4–30.6)	27.3 (25.1–30.7)	0.659	0.833
SBP (mmHg)	137.5 ± 25.1	136.2 ± 25.4	133.0 ± 23.4	132.9 ± 23.3	135.1 ± 23.3	136.2 ± 23.5	0.505	0.663
DBP (mmHg)	86.6 ± 19.2	86.0 ± 18.8	81.8 ± 16.4	82.3 ± 16.4	80.5 ± 17.0	80.6 ± 17.8	0.067	0.215
Heart rate (beats/minute)	74.0 ± 17.3	72.8 ± 18.8	71.9 ± 14.8	72.3 ± 14.9	71.2 ± 14.6	71.3 ± 14.7	0.487	0.878
Cr clearance (ml/minute/1.73 m^2)	98.1 ± 28.1	101.6 ± 26.4	93.4 ± 29.1	93.8 ± 30.0	92.7 ± 25.6	93.9 ± 26.1	0.401	0.190
Medication on admission								
Beta-blocker	6/82 (7.3)	4/63 (6.3)	6/79 (7.6)	6/69 (8.7)	6/86 (7.0)	3/65 (4.6)	0.988	0.633
ACE inhibitor/A2RB	14/82 (17.1)	7/63 (11.1)	17/79 (21.5)	16/69 (23.2)	13/86 (15.1)	12/65 (18.5)	0.549	0.190
Statin	17/82 (20.7)	14/63 (22.2)	25/79 (31.6)	19/69 (27.5)	13/86 (15.1)	7/65 (10.8)	0.036	0.049

continued

TABLE 7 Demography of the total trial population and the CMR treatment groups[a] (*continued*)

Characteristics	Adenosine		SNP		Control		*p*-value	
	All ($n = 82$)	With CMR data ($n = 63$)	All ($n = 79$)	With CMR data ($n = 69$)	All ($n = 86$)	With CMR data ($n = 65$)	All	With CMR data
IRA								
LAD – proximal	19/82 (23.2)	11/63 (17.5)	18/79 (22.8)	16/69 (23.2)	20/86 (23.3)	15/65 (23.1)	0.997	0.663
LAD – other	13/82 (15.9)	12/63 (19.0)	15/79 (19.0)	12/69 (17.4)	14/86 (16.3)	12/65 (18.5)	0.848	0.969
LCX	10/82 (12.2)	6/63 (9.5)	13/79 (16.5)	13/69 (18.8)	18/86 (20.9)	12/65 (18.5)	0.314	0.259
RCA	40/82 (48.8)	34/63 (54.0)	33/79 (41.8)	28/69 (40.6)	34/86 (39.5)	26/65 (40.0)	0.455	0.197
TFG								
0–1	80/81 (98.8)	61/62 (98.4)	72/79 (91.1)	63/69 (91.3)	83/86 (96.5)	62/65 (95.4)	0.057	0.180
2	1/81 (1.2)	1/62 (1.6)	5/79 (6.3)	5/69 (7.2)	1/86 (1.2)	1/65 (1.5)	0.078	0.124
3	0/81 (0.0)	0/62 (0.0)	2/79 (2.5)	1/69 (1.4)	2/86 (2.3)	2/65 (3.1)	0.367	0.368
Thrombus score								
4–5	75/81 (92.6)	57/62 (91.9)	72/79 (91.1)	64/69 (92.8)	81/86 (94.2)	60/65 (92.3)	0.754	0.985

A2RB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; Cr, creatinine; DBP, diastolic blood pressure; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; SBP, systolic blood pressure.

a Values are mean ± SD, median (interquartile range) or *n*/*N* (%).

TABLE 8 Procedural data and intraprocedural complications according to treatment group[a]

Characteristics	Adenosine (all subjects) ($n = 82$)	SNP (all subjects) ($n = 79$)	Control (all subjects) ($n = 86$)	*p*-value[b]	*p*-value[c]
Procedural data					
Femoral approach	12 (14.6)	9 (11.4)	7 (8.1)	0.184	0.481
Radial approach	70 (85.4)	70 (88.6)	79 (91.9)	0.184	0.481
Thrombectomy	81 (98.8)	75 (98.7)[d]	80 (93.0)	0.118	0.122
DES implantation	73 (89.0)	72 (91.1)	81 (94.2)	0.226	0.452
Number of stents, median (IQR)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.613	0.790
Diameter of stented segment (mm), median (IQR)	3.5 (3.0–3.5)	3.5 (3.0–3.5)	3.0 (3.0–3.5)	0.465	0.649
Length of stented segment (mm), median (IQR)	26.0 (18.0–39.0)	23.0 (18.0–38.0)	24.0 (18.0–34.5)	0.585	0.833
Intraprocedural complications					
Transient AV block not requiring pacing	7 (8.5)	2 (2.5)	10 (11.6)	0.507	0.034
AV block requiring pacing	2 (2.4)	1 (1.3)	0 (0.0)	0.237	0.479
Transient hypotension not requiring vasopressor drugs or IABP	5 (6.1)	13 (16.5)	5 (5.8)	0.938	0.028
Hypotension requiring vasopressor drugs or IABP	5 (6.1)	3 (3.8)	6 (7.0)	0.818	0.499
Ventricular tachycardia/ fibrillation	5 (6.1)	3 (3.8)	5 (5.8)	0.938	0.722

AV, atrioventricular; DES, drug-eluting stent; IABP, intra-aortic balloon pump; IQR, interquartile range.
a Values are mean ± SD or *n* (%) unless stated otherwise.
b Adenosine vs. control.
c SNP vs. control.
d The denominator is not 79 as these data were missing for three patients.

Cardiac magnetic resonance imaging assessment of myocardial injury

Cardiac magnetic resonance imaging characteristics of the study population are presented by treatment arm in *Table 10*. There was no statistically significant difference in the primary outcome measure of unadjusted infarct size (%LVM) between the adenosine- or SNP-facilitated PPCI groups and the control group. 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% 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 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 also appeared higher in the adenosine-treated arm than in the control arm, although, again, this was not statistically significant. Other CMR 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.

TABLE 9 Angiographic, electrocardiographic and enzymatic data according to treatment group[a]

Characteristics	Adenosine (all subjects) ($n = 82$)	SNP (all subjects) ($n = 79$)	Control (all subjects) ($n = 86$)	*p*-value[b]	*p*-value[c]
Angiographic					
Final TFG < 3	4 (4.9)	6 (7.6)	3 (3.5)	0.652	0.313
Final TMPG 0–1	0 (0.0)	1 (1.3)	1 (1.2)	0.327	1.000
Quantitative MBG	10.0 (7.0–14.0)	11.0 (7.0–17.8)	12.0 (8.0–17.0)	0.144	0.481
Final cTFC	14.0 (9.0–20.0)	14.0 (10.0–21.0)	15.0 (10.0–22.0)	0.457	0.928
Electrocardiographic					
Baseline maximal sum of ST-segment elevation	9.0 (6.0–12.0)	9.0 (5.0–13.0)	9.0 (5.0–13.0)	0.931	0.686
Post-PPCI maximal sum of ST-segment elevation	2.0 (0.0–5.0)	2.0 (0.0–5.0)	2.0 (0.0–4.0)	0.684	0.472
STR > 70%	56 (68.3)	48 (60.8)	56 (65.1)	0.662	0.562
Enzymatic					
Peak CK (mg/dl)	1559 (601–2804)	1171 (430–2259)	1336 (511–2632)	0.601	0.393

CK, creatine kinase.
a Values are *n* (%) or median (interquartile range).
b Adenosine vs. control.
c SNP vs. control.

TABLE 10 Cardiac magnetic resonance data according to treatment group[a]

Characteristics	Adenosine	SNP	Control	*p*-value[b]	*p*-value[c]
Scar assessment[d]	$n = 63$	$n = 69$	$n = 65$		
Infarct size (%LVM)	10.1 (4.7–16.2)	10.0 (4.2–15.8)	8.3 (1.9–14.0)	0.062	0.160
Microvascular injury	$n = 63$	$n = 69$	$n = 65$		
Presence of IMH, *n/N* (%)	20/38 (52.6)	19/43 (44.2)	16/38 (42.1)	0.358	0.850
Presence of early MVO, *n/N* (%)	41/60 (68.3)	42/59 (71.2)	38/63 (60.3)	0.452	0.254
Presence of late MVO, *n/N* (%)	43/63 (68.3)	52/69 (75.4)	37/65 (56.9)	0.205	0.029
Early MVO (%LVM)	1.2 (0.0–5.2), $n = 60/82$	1.0 (0.0–5.0), $n = 59/79$	1.4 (0.0–4.3), $n = 63/86$	0.637	0.770
Late MVO (%LVM)	1.0 (0.0–3.7)	0.6 (0.0–2.4)	0.3 (0.0–2.8)	0.205	0.244
Salvage	$n = 34$	$n = 38$	$n = 37$		
AAR (%LVM)	30.6 ± 12.2	34.7 ± 14.4	30.3 ± 11.5	0.907	0.152
MSI (%)	60.2 ± 23.3	63.6 ± 24.7	67.5 ± 23.3	0.188	0.477
Function and volumes	$n = 63$	$n = 71$	$n = 68$		
LVEDVI (ml/m^2)	91.3 ± 16.1	87.0 ± 16.9	84.4 ± 14.6	0.011	0.336
LVESVI (ml/m^2)	52.3 ± 13.8	49.1 ± 12.7	46.1 ± 11.6	0.006	0.155
LVMI (g/m^2)	59.1 ± 11.5	56.0 ± 11.2	53.6 ± 9.2	0.003	0.174
LVEF (%)	43.2 ± 7.9	43.9 ± 6.5	45.7 ± 8.0	0.080	0.165

EF, ejection fraction; LVEDVI, LV end-diastolic volume indexed to body surface area; LVESVI, LV end-systolic volume indexed to body surface area; LVMI, LVM indexed to body surface area.
a Values are mean $\pm$ SD or median (interquartile range) unless otherwise stated.
b Adenosine vs. control.
c SNP vs. control.
d Primary end point – comparison using an independent *t*-test on a log-transformed scale.

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 control arms.

Diagnostic quality T2w-STIR (oedema) imaging, required for AAR estimation and derivation of MSI, was obtainable in only 109 patients (55%). In patients who had oedema assessed, there was no significant difference between the groups in myocardial salvage.

Echocardiography

Echocardiography was performed at 3 months in 108 subjects (44%) ($n = 44$ 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 the SNP arm (51.5, 45.0–61.0; $p = 0.015$).

Clinical outcomes

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). An overview of clinical events is presented in *Table 11*. There was a significant increase in MACEs in patients undergoing adenosine-facilitated PPCI compared with control patients, driven by heart failure, at 30 days (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 and the low bleeding event rate is consistent with the use of predominantly radial vascular access and bivalirudin in this study.

TABLE 11 Clinical events to 6 months according to treatment group[a]

Characteristics	Adenosine (all subjects) ($n = 82$)	SNP (all subjects) ($n = 79$)	Control (all subjects) ($n = 86$)	*p*-value[b]	*p*-value[c]
First event					
MACE	12 (14.6)	5 (6.3)	2 (2.3)	0.01	0.261
Death	1 (1.2)	1 (1.3)	0 (0.0)	0.488	0.479
CVE	1 (1.2)	1 (1.3)	0 (0.0)	0.488	0.479
MI	2 (2.4)	1 (1.3)	1 (1.2)	0.614	1.000
HF	8 (9.8)	2 (2.5)	1 (1.2)	0.016	0.607
TLR	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000
Composite of death, MI and HF	11 (13.4)	4 (5.1)	2 (2.3)	0.009	0.428
Number of patients with > 1 event	3 (3.7)	1 (1.3)	1 (1.2)	0.359	1.000
Bleeding					
All bleeding	4 (4.9)	2 (2.5)	5 (5.8)	1.000	0.446
Fatal bleeding	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000

CVE, cerebrovascular event; HF, heart failure; TLR, target lesion revascularisation.
a Values are *n* (%).
b Adenosine vs. control.
c SNP vs. control.

Kaplan–Meier graphs of time to first MACE are shown in *Figure 3*. When adjusted for confounders (age, sex, diabetes, anterior MI, ischaemia time and Rentrop score), the observed effect remains, with similar HRs and log-rank $p = 0.018$ at 30 days and $p = 0.01$ at 6 months (see *Table 14*).

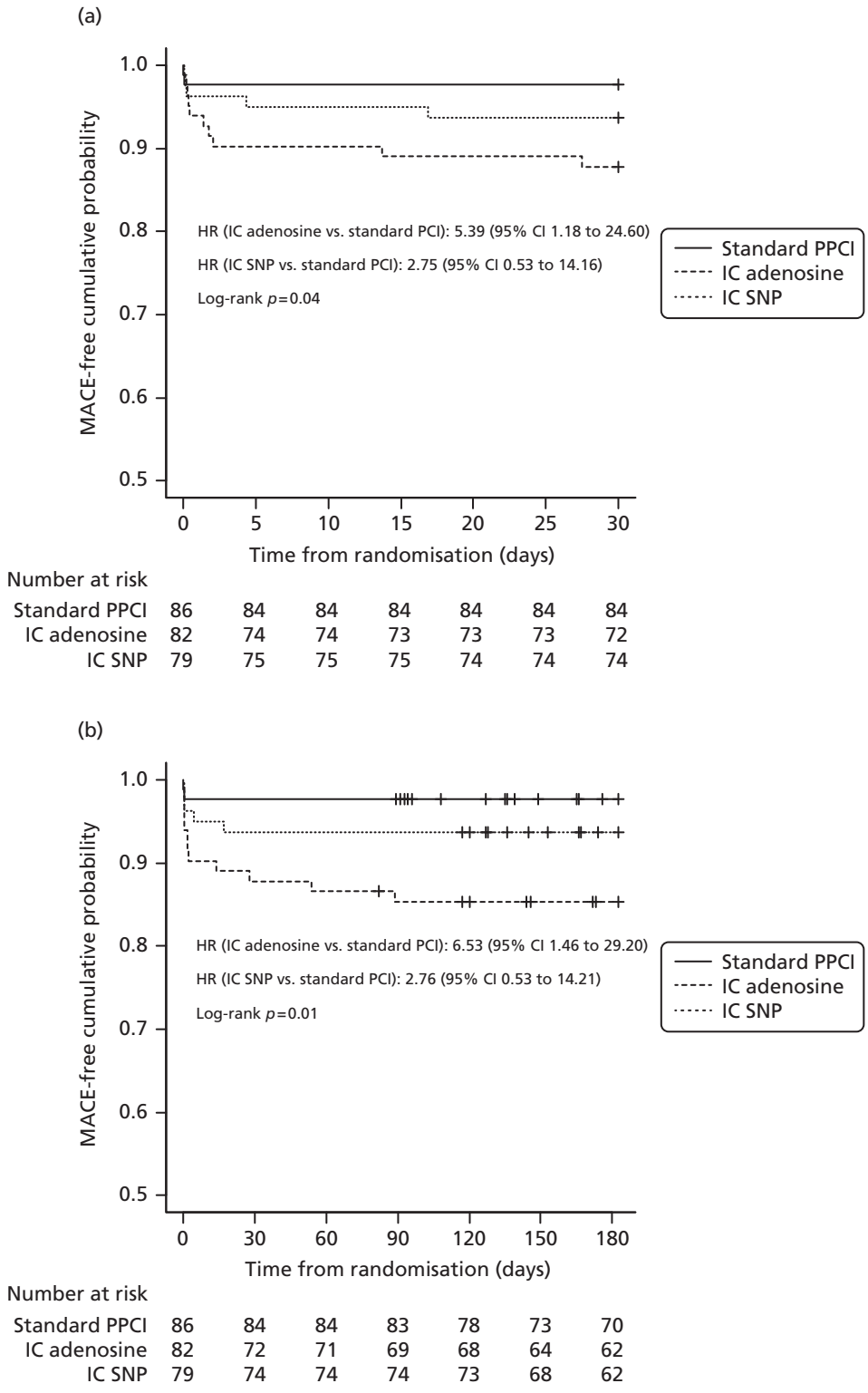

FIGURE 3 Kaplan–Meier graphs showing clinical outcome in the three treatment arms at 30 days and 6 months (ITT). (a) Time to first MACE within 30 days; and (b) time to first MACE (median follow-up 6 months).

Per-protocol analysis

We observed a high rate of failed study drug delivery in the adenosine and SNP arms (*Table 12*). Almost one in five patients randomised to drug-facilitated PPCI did not receive the second dose of the study drug post stent deployment as a result of an increased QTc following the first dose. Consequently, secondary analysis per protocol was performed (*Table 13*)

Patients in the adenosine arm who received both doses of the study drug 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 a reduced ejection fraction were also observed in the adenosine arm.

Considering only patients who received both doses of the study drug and plotting Kaplan–Meier graphs for time to first MACE again shows a statistically significantly increased HR for adenosine-facilitated PPCI compared with the control at 30 days (HR 5.91, 95% 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 (*Figure 4*).

TABLE 12 Failure of study drug administration

Reason study drug not administered	*n* (%)
First dose	**N = *161***
Hypotension	3 (1.9)
Unable to cross lesion	3 (1.9)
Coronary dissection	1 (0.6)
Total	7 (4.3)
Second dose	**N = *155***
Prolonged or > 60-millisecond increase in QTc	30 (19.4)
Coronary dissection	1 (0.6)
Ventricular fibrillation	1 (0.6)
No stent deployed	1 (0.6)
Other SAE (operator decision)	1 (0.6)
Total	34 (21.9)
Either first or second dose	**N = *161***
Prolonged or > 60-millisecond increase in QTc	30 (18.6)
Hypotension	3 (1.9)
Unable to cross lesion	3 (1.9)
Coronary dissection	2 (1.2)
Ventricular fibrillation	1 (0.6)
No stent deployed	1 (0.6)
Other SAE (operator decision)	1 (0.6)
Total	41 (25.5)

SAE, serious adverse event.

TABLE 13 Main data according to treatment group: per-protocol analysis[a]

Characteristics	Adenosine ($N = 66$)	SNP ($N = 53$)	Control ($N = 86$)	p-value[b]	p-value[c]
Angiographic					
Quantitative MBG	11.0 (7.0–14.0)	11.0 (7.0–15.0)	12.0 (8.0–17.0)	0.165	0.134
Final cTFC	14.0 (9.0–21.0)	15.0 (10.0–21.0)	15.0 (10.0–22.0)	0.639	0.909
Echocardiographic					
LVEF (3 months) (%)	53.0 (40.0–60.0)	54.0 (45.0–61.0)	58.5 (54.5–64.0)	0.006	0.038
Electrocardiographic					
STR > 70%, *n* (%)	46 (69.7)	28 (52.8)	56 (65.1)	0.604	0.158
Enzymatic					
Peak CK (mg/dl)	1664 (788–2886)	1333 (578–2247)	1336 (511–2632)	0.253	0.387
CMR data					
Function and volumes	$n = 52$	$n = 48$	$n = 68$		
LVEDVI (ml/m^2)	91.4 ± 14.1	87.3 ± 16.3	84.4 ± 14.6	0.009	0.304
LVESVI (ml/m^2)	52.7 ± 11.6	49.0 ± 12.6	46.1 ± 11.6	0.003	0.203
LVMI (g/m^2)	59.9 ± 11.5	56.7 ± 11.4	53.6 ± 9.2	0.001	0.109
LVEF (%)	42.5 ± 7.2	44.3 ± 6.8	45.7 ± 8.0	0.029	0.332
Salvage	$n = 30$	$n = 26$	$n = 37$		
AAR (%LVM)	31.6 ± 10.9	34.7 ± 14.4	30.3 ± 11.5	0.639	0.147
MSI (%)	59.0 ± 22.1	63.6 ± 24.7	67.5 ± 23.3	0.134	0.544
Microvascular injury	$n = 52$	$n = 47$	$n = 65$		
Presence of IMH, *n/N* (%)	19/33 (57.6)	14/30 (46.7)	16/38 (42.1)	0.238	0.807
Presence of early MVO, *n/N* (%)	35/49 (71.4)	31/42 (73.8)	38/63 (60.3)	0.238	0.208
Presence of late MVO, *n/N* (%)	38/52 (73.1)	37/47 (78.7)	37/65 (56.9)	0.083	0.025
Early MVO (%LVM)	1.6 (0.0–5.3), $n = 49/66$	0.9 (0.0–3.3), $n = 42/53$	1.4 (0.0–4.3), $n = 63/86$	0.506	0.960
Late MVO (%LVM)	1.2 (0.0–3.7)	0.6 (0.0–2.3)	0.3 (0.0–2.8)	0.106	0.345
Scar assessment	$n = 52$	$n = 47$	$n = 65$		
Infarct size (%LVM)[d]	12.0 (4.8–16.5)	10.0 (7.3–13.8)	8.3 (1.9–14.0)	0.031	0.088
First event,* n *(%)	**N = *66***	**N = *53***	**N = *86***		
MACE	10 (15.2)	3 (5.7)	2 (2.3)	0.005	0.369
Death	0 (0.0)	1 (1.9)	0 (0.0)	1.000	0.381
CVE	1 (1.5)	1 (1.9)	0 (0.0)	0.434	0.381
MI	2 (3.0)	0 (0.0)	1 (1.2)	0.580	1.000
HF	7 (10.6)	1 (1.9)	1 (1.2)	0.021	1.000
TLR	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000
Composite of death, MI and HF	9 (13.6)	2 (3.8)	2 (2.3)	0.010	0.636

CVE, cerebrovascular event; EF, ejection fraction; HF, heart failure; LVEDVI, LV end-diastolic volume indexed to body surface area; LVESVI, LV end-systolic volume indexed to body surface area; LVMI, LVM indexed to body surface area; TLR, target lesion revascularisation.

a Values are mean ± SD or median (IQR) unless otherwise stated.

b Adenosine vs. control.

c SNP vs. control.

d Primary end point – comparison using an independent *t*-test on a log-transformed scale.

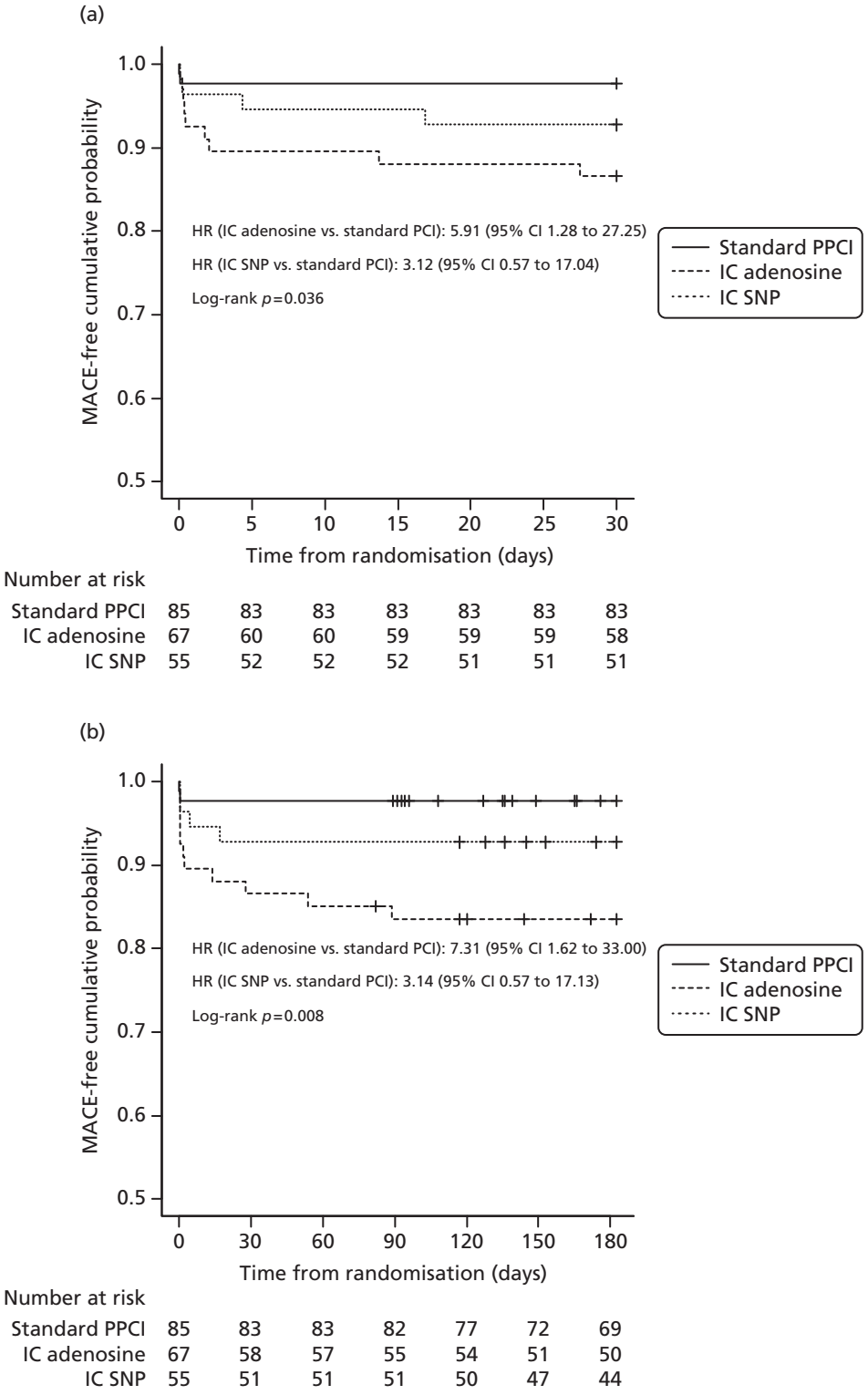

FIGURE 4 Kaplan–Meier graphs showing clinical outcome in the three treatment arms at 30 days and 6 months in patients treated per protocol. (a) Time to first MACE within 30 days; and (b) time to first MACE (median follow-up 6 months).

Survival analysis demonstrated a clear signal of increased hazard with adenosine-facilitated PPCI compared with the control (*Table 14*). Our clinical outcome data are consistent with the CMR imaging data (increased LV volumes, reduced ejection fraction and increased infarct size), which together suggest possible adverse LV remodelling with adenosine treatment leading to worse clinical outcomes than with standard PPCI (control).

TABLE 14 Major adverse cardiac events at 30 days and 6 months by ITT and per-protocol analysis

Analysis	Adjusted or unadjusted	Comparison	HR	95% CI	*p*-value	Log-rank *p*-value
First MACE within 30 days						
ITT	Unadjusted	Adenosine vs. control	5.39	1.18 to 24.60	0.03	0.04
		SNP vs. control	2.75	0.53 to 14.16	0.2	
	Adjusted[a]	Adenosine vs. control	5.24	1.13 to 24.33	0.03	0.018
		SNP vs. control	2.36	0.45 to 12.40	0.3	
Per protocol	Unadjusted	Adenosine vs. control	5.91	1.28 to 27.25	0.02	0.036
		SNP vs. control	3.12	0.57 to 17.04	0.2	
	Adjusted[a]	Adenosine vs. control	5.76	1.21 to 27.35	0.03	0.1
		SNP vs. control	2.94	0.52 to 16.60	0.2	
First MACE after 6 months' median follow-up						
ITT	Unadjusted	Adenosine vs. control	6.53	1.46 to 29.20	0.01	0.01
		SNP vs. control	2.76	0.53 to 14.21	0.2	
	Adjusted[a]	Adenosine vs. control	6.54	1.45 to 29.64	0.01	0.01
		SNP vs. control	2.53	0.48 to 13.24	0.3	
Per protocol	Unadjusted	Adenosine vs. control	7.31	1.62 to 33.00	0.01	0.008
		SNP vs. control	3.14	0.57 to 17.13	0.2	
	Adjusted[a]	Adenosine vs. control	7.32	1.59 to 33.59	0.01	0.05
		SNP vs. control	3.20	0.57 to 18.01	0.2	

a Adjusted for age, sex, diabetes, anterior MI, ischaemia time and Rentrop score.

Chapter 5 Discussion

The REFLO-STEMI trial was designed to test whether adjunctive pharmacotherapy with adenosine and/or SNP could reduce the extent of myocardial injury (infarct size and MVO) as measured by the sensitive CMR surrogate markers and, additionally, as a secondary end point, improve clinical outcome. In the introduction the theoretical case for benefit of these agents was made. There is good basic science and preclinical evidence that both drugs have the potential to attenuate the MVO process. The REFLO-STEMI study is the first study to combine what are considered appropriate drug dosages, delivered optimally to the site of maximal benefit, with the use of CMR imaging to robustly measure reperfusion success and scar size in a group of patients treated with a contemporary reperfusion strategy. The study was powered accordingly to deliver a definitive answer to the question of whether these agents can reduce infarct size. Additional measures of myocardial perfusion (angiographic and electrocardiographic) and early clinical outcome data provide further insight into the potential role of prophylactic adjunctive pharmacotherapy administered universally for STEMI patients.

The trial was designed to ensure that account was taken of potential safety parameters. Thus, prolongation of the QTc after the first dose resulted in the second dose not being given in 19% of patients. This had some impact on the numbers in the two groups who completed the treatment strategy, with only 66 of 82 (80%) patients in the adenosine group receiving both doses and only 53 of 79 (67%) patients in the SNP group receiving both doses. All results are therefore presented as ITT analyses, as per the statistical analysis plan, but also as per-protocol analyses.

Baseline characteristics and procedural detail

The groups were well matched in terms of baseline demographics in the trial overall and in those who completed the CMR scan (see *Table 7*). There tended to be more diabetic patients in the SNP group but this was not significant. There was a significant excess of patients with hypercholesterolaemia in both treatment groups compared with the control group and to be expected a greater use of statins in these patients. There were no differences between the groups in important potential confounders such as age, site of infarct and total ischaemic time. As per the inclusion criteria most patients had TFG 0–1 at first angiography.

In keeping with a study undertaken in expert centres there was a high rate of use of the radial approach and a very high rate of drug-eluting stent usage, consistent with contemporary practice. Thrombectomy was mandated as the device was subsequently used for local delivery of the drug and so the rate of thrombectomy was high in each group. It is interesting to note that mean stent length was 23–26 mm. Intraprocedural complications are shown in *Table 8*. We expected there to be a high incidence of AV block in the adenosine group but this was higher (albeit not requiring pacing) in the control group. We suspect that this is because of the natural incidence of AV block in such patients and we should note that a proportion of the adenosine and SNP patients did not receive a second dose. Even so, this cannot be the cause of the findings and so they must be regarded as a play of chance. Transient hypotension not requiring resuscitative therapy was significantly higher in the SNP group and this may be a more expected finding given the profound vasodilating properties of SNP.

Angiographic and electrocardiographic outcomes

Again, in keeping with a study undertaken in high-volume expert centres, the number of participants with a final TFG of < 3 was in single digits (see *Table 9*). Importantly, despite the basic science and observational data,[46,63,66,121–127] there was no difference in this or other markers of microvascular blood flow (final TMPG, quantitative MBG, final cTFC) between the treatment groups or between either treatment

group and the control group. This is consistent with some[42,44,51,52] but not all[44,53,60,61,128,129] randomised trials. Similarly, a surrogate marker of flow (resolution of ECG peak elevation to > 70%) was seen to be similar in all three groups and was relatively high at 68.3%, 60.8% and 65.1% compared with previous studies,[44,51–53,129] probably reflecting the fact that recruitment was limited to those with a time from symptoms to presentation of ≤ 6 hours. All of these markers are of course surrogates of flow and infarct size that are less sensitive than our chosen end point.

Primary end point: infarct size and other cardiac magnetic resonance imaging markers of reperfusion injury

Of the trial population, 20% of patients did not undergo the CMR assessment. The main reasons for exclusion were early repatriation to a secondary care hospital (before CMR assessment could be undertaken), lack of consent and patients being too unwell. Those completing the CMR assessment had similar characteristics to those not completing the assessment (see *Table 7*).

The main finding was that there was no significant difference in infarct size between the groups, although when the results were adjusted for infarct location there was a borderline significant increase in infarct size in the adenosine group compared with the control group. Certainly, neither drug reduced infarct size. Additionally, there was no decrease in MSI, early MVO or late MVO, indicating a lack of efficacy of adenosine and SNP in terms of preventing reperfusion injury. These results are consistent with those of the only other randomised trial that included CMR imaging;[51] this trial also did not show any benefit of high-dose IC adenosine. It is interesting to note that the adenosine-treated patients had increased myocardial volumes and a non-significant trend towards a reduced ejection fraction compared with the control group. The per-protocol analysis actually showed that patients who received both doses of adenosine had an increased infarct size, increased LV volumes and a reduced ejection fraction (also seen on follow-up echocardiography) on CMR imaging compared with the control group, which suggests not only a lack of efficacy but also potential adverse effects on reperfusion.

Clinical outcomes

Clinical events were included in the study as an important safety consideration but the trial was not powered to detect clinically meaningful differences in MACEs between groups. However, clinical outcome was incidentally found to be significantly worse for the adenosine group than the control group (see *Table 11*), largely driven by increased early heart failure events. Although this finding may have occurred by chance and was not shown in previous trials, the HR is high, it fits with the infarct size measures being increased and is consistent whether assessed in ITT or in per-protocol analysis, at 1 and 6 months' follow-up and after adjustment for potential confounding variables (age, sex, ischaemia time, diabetes, anterior MI or not and Rentrop score). Taken together with the CMR findings, the results suggest that using adenosine to *protect* against MVO and its potential clinical consequence not only fails to do so but may also in fact have significant clinical adverse outcomes. This finding of an adverse effect of adenosine remains difficult to explain. One possible explanation is that ischaemia already induces high levels of endogenous adenosine[51,130] and that further doses, particularly high doses, have no additional benefits and possibly detrimental effects because of distal embolisation, hypotension and bradycardia, although we did not see any significant differences in these parameters in this study. The finding is hypothesis generating. High-dose IC adenosine should not be used in the setting of PPCI to prevent reperfusion injury. Whether this applies to IC adenosine given for angiographic clear no-reflow remains contentious, as the risk/benefit ratio may be different.

Limitations

The study was open label and this may have influenced the management of patients, particularly at the time of PPCI; however, the primary outcome was assessed on blinded CMR scans. A major limitation of T2w-STIR imaging for AAR is that the sequence is prone to artefacts and oedema may not be discernible. In one previous study T2w-STIR identified only 64% of culprit arteries in 54 acute STEMI patients and the AAR was less than the amount of LGE in 30% of patients.[131] In our recently published CMR substudy of CvLPRIT (Complete versus culprit-Lesion only PRimary PCI Trial), the AAR was only quantifiable in 75% of the 203 patients who completed the baseline CMR assessment at 1.5T.[132] In this study, using 3.0T CMR with greater field inhomogeneity and the early scanning of patients post STEMI, diagnostic quality T2w-STIR imaging was obtainable in only 55% of patients who completed the CMR assessment. In at least one other multicentre trial with core laboratory analysis, T2w imaging obtained an even lower rate of analysable images for oedema (≈50%) than we have reported.[133] Although issues with T2w-STIR are well recognised,[134] in multicentre trials this sequence is still frequently used as the newer T1 and T2 mapping sequences, which appear to be more robust for AAR detection, are not widely available. However, given the importance of the MSI in the comparison of therapies in STEMI, such sequences should be used in future studies.

A mechanistic substudy evaluating periprocedural platelet activity was planned but had to be abandoned because of a lack of sufficient data (partly because of staffing issues including staff pregnancy) to make any significant scientific statement.

The trial assessed whether or not MVO could be attenuated prior to PPCI and our negative results do not imply that SNP and adenosine are ineffective if no-reflow occurs post PPCI.

Recommendations for research

Studies undertaken in the modern PPCI era have collectively shown a failure of therapies underpinned by an extensive body of positive experimental data to prophylactically reduce MVO or infarct size. Future trials could perhaps focus on limiting reperfusion injury when angiographic slow-flow/no-reflow is encountered, utilising robust end points as in our study.

The MSI measures reperfusion success and predicts prognosis post STEMI.[103] The MSI requires accurate assessment of myocardial oedema and AAR. Oedema is typically imaged on pre-contrast T2w-STIR imaging, as used in our study, but its use is hampered by its susceptibility to artefacts.[135] We note that there was a failure rate of 45% in achieving accurate oedema assessment in our study. This may have been exacerbated by the use of 3.0T CMR imaging in our study but nonetheless should caution the general MRI community against using T2w-STIR for routine oedema assessment following STEMI. Pre-contrast T1 mapping on CMR may be superior to T2w-STIR for the identification of reversible myocardial injury and prediction of functional recovery in acute MI.[136] Using the former technique to detect myocardial oedema and evaluate CMR surrogate markers of myocardial injury in future studies may also reduce the sample sizes required[137] and this should perhaps be the first-choice CMR imaging technique for assessing AAR and MSI post STEMI in future trials.

Chapter 6 Conclusions

The REFLO-STEMI trial was a well-designed trial that tested two drugs, adenosine and SNP, in appropriate doses and delivered locally, using a sensitive marker (CMR imaging) of the potential impact of these drugs on flow and therefore infarct size. If these drugs were beneficial this trial should have shown it. There was no demonstrated efficacy with either drug, a finding that will inform the interventional community. Indeed, we will ask the community to note the adverse effects in the adenosine group. Outcomes after PPCI are still far from optimal and this was an attempt to see whether adjunctive pharmacotherapy delivered optimally would improve outcomes. As such, it was an important and worthy, albeit challenging, study.

We conclude that neither adenosine nor SNP reduce infarct size or reperfusion injury when administered during PPCI treatment of STEMI. Furthermore, use of high-dose adenosine in STEMI may cause cardiac toxicity and worsen clinical outcome. Current STEMI guidelines advocate the use of adenosine in established angiographic MVO (slow-flow/no-reflow) and clinicians frequently give repeated doses of adenosine in this setting. Our results should strongly discourage clinicians from using cumulatively high doses of IC adenosine during PPCI to prevent reperfusion injury.

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Contributions of authors

Sheraz A Nazir prepared the final report, which all authors read and approved.

Sheraz A Nazir, **Jamal N Khan**, **John P Greenwood**, **Daniel J Blackman**, **Vijay Kunadian**, **Martin Been** and **Anthony H Gershlick** were responsible for patient recruitment.

Islam Z Mahmoud, **Gerry P McCann** and **Anthony H Gershlick** conceived the idea for the study.

Sheraz A Nazir, **Islam Z Mahmoud**, **John P Greenwood**, **Daniel J Blackman**, **Gerry P McCann** and **Anthony H Gershlick** designed the study and developed protocols.

Vijay Kunadian was responsible for analysing all angiograms.

Sheraz A Nazir and **Keith R Abrams** performed all statistical analyses.

Robert Wilcox chaired the TSC and **AA Jennifer Adgey** chaired the DSMB.

Islam Z Mahmoud, **John P Greenwood**, **Daniel J Blackman**, **Keith R Abrams**, **Gerry P McCann** and **Anthony H Gershlick** prepared the funding application.

Sheraz A Nazir and **Gerry P McCann** were responsible for all CMR analyses.

John P Greenwood, **Daniel J Blackman**, **Keith R Abrams**, **Gerry P McCann** and **Anthony H Gershlick** also had TSC membership.

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Data sharing statement

All available trial data can be obtained by request to the corresponding author.

References

1. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology, Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**:2569–619. http://dx.doi.org/10.1093/eurheartj/ehs215
2. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;**361**:13–20. http://dx.doi.org/10.1016/S0140-6736(03)12113-7
3. Kloner RA, Ganote CE, Jennings RB. The 'no-reflow' phenomenon after temporary coronary occlusion in the dog. *J Clin Invest* 1974;**54**:1496–508. http://dx.doi.org/10.1172/JCI107898
4. Braunwald E, Kloner RA. Myocardial reperfusion: a double-edged sword? *J Clin Invest* 1985;**76**:1713–19. http://dx.doi.org/10.1172/JCI112160
5. Harlan JM. Leukocyte–endothelial interactions. *Blood* 1985;**65**:513–25.
6. McCord JM. Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med* 1985;**312**:159–63. http://dx.doi.org/10.1056/NEJM198501173120305
7. Engler R, Covell JW. Granulocytes cause reperfusion ventricular dysfunction after 15-minute ischemia in the dog. *Circ Res* 1987;**61**:20–8. http://dx.doi.org/10.1161/01.RES.61.1.20
8. Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation* 2000;**101**:570–80. http://dx.doi.org/10.1161/01.CIR.101.5.570
9. Gersh BJ. Optimal management of acute myocardial infarction at the dawn of the next millennium. *Am Heart J* 1999;**138**:S188–202. http://dx.doi.org/10.1016/S0002-8703(99)70342-X
10. Kotani J, Nanto S, Mintz GS, Kitakaze M, Ohara T, Morozumi T, *et al.* Plaque gruel of atheromatous coronary lesion may contribute to the no-reflow phenomenon in patients with acute coronary syndrome. *Circulation* 2002;**106**:1672–7. http://dx.doi.org/10.1161/01.CIR.0000030189.27175.4E
11. Araszkiewicz A, Grajek S, Lesiak M, Prech M, Pyda M, Janus M, *et al.* Effect of impaired myocardial reperfusion on left ventricular remodeling in patients with anterior wall acute myocardial infarction treated with primary coronary intervention. *Am J Cardiol* 2006;**98**:725–8. http://dx.doi.org/10.1016/j.amjcard.2006.04.009
12. Galiuto L, Lombardo A, Maseri A, Santoro L, Porto I, Cianflone D, *et al.* Temporal evolution and functional outcome of no reflow: sustained and spontaneously reversible patterns following successful coronary recanalisation. *Heart* 2003;**89**:731–7. http://dx.doi.org/10.1136/heart.89.7.731
13. Rezkalla SH, Dharmashankar KC, Abdalrahman IB, Kloner RA. No-reflow phenomenon following percutaneous coronary intervention for acute myocardial infarction: incidence, outcome, and effect of pharmacologic therapy. *J Interv Cardiol* 2010;**23**:429–36. http://dx.doi.org/10.1111/j.1540-8183.2010.00561.x
14. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP, *et al.* Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. *Circulation* 1998;**97**:765–72. http://dx.doi.org/10.1161/01.CIR.97.8.765
15. Wu KC, Kim RJ, Bluemke DA, Rochitte CE, Zerhouni EA, Becker LC, *et al.* Quantification and time course of microvascular obstruction by contrast-enhanced echocardiography and magnetic resonance imaging following acute myocardial infarction and reperfusion. *J Am Coll Cardiol* 1998;**32**:1756–64. http://dx.doi.org/10.1016/S0735-1097(98)00429-X

16. Hombach V, Grebe O, Merkle N, Waldenmaier S, Höher M, Kochs M, *et al.* Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging. *Eur Heart J* 2005;**26**:549–57. http://dx.doi.org/10.1093/eurheartj/ehi147

17. Nijveldt R, Beek AM, Hirsch A, Stoel MG, Hofman MB, Umans VA, *et al.* Functional recovery after acute myocardial infarction: comparison between angiography, electrocardiography, and cardiovascular magnetic resonance measures of microvascular injury. *J Am Coll Cardiol* 2008;**52**:181–9. http://dx.doi.org/10.1016/j.jacc.2008.04.006

18. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, *et al.* Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet* 2008;**371**:1915–20. http://dx.doi.org/10.1016/S0140-6736(08)60833-8

19. Sardella G, Mancone M, Bucciarelli-Ducci C, Agati L, Scardala R, Carbone I, *et al.* Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial. *J Am Coll Cardiol* 2009;**53**:309–15. http://dx.doi.org/10.1016/j.jacc.2008.10.017

20. Liistro F, Grotti S, Angioli P, Falsini G, Ducci K, Baldassarre S, *et al.* Impact of thrombus aspiration on myocardial tissue reperfusion and left ventricular functional recovery and remodeling after primary angioplasty. *Circ Cardiovasc Interv* 2009;**2**:376–83. http://dx.doi.org/10.1161/CIRCINTERVENTIONS.109.852665

21. Stone GW, Maehara A, Witzenbichler B, Godlewski J, Parise H, Dambrink J-HE, *et al.* Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. *JAMA* 2012;**307**:1817–26. http://dx.doi.org/10.1001/jama.2012.421

22. Dudek D, Mielecki W, Burzotta F, Gasior M, Witkowski A, Horvath IG, *et al.* Thrombus aspiration followed by direct stenting: a novel strategy of primary percutaneous coronary intervention in ST-segment elevation myocardial infarction. Results of the Polish-Italian-Hungarian randomized thrombectomy trial (PIHRATE trial). *Am Heart J* 2010;**160**:966–72. http://dx.doi.org/10.1016/j.ahj.2010.07.024

23. Frobert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, *et al.* Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013;**369**:1587–97. http://dx.doi.org/10.1056/NEJMoa1308789

24. Tomassini F, Gagnor A, Montali N, Gambino A, Bollati M, Infantino V, *et al.* Impact of thrombus aspiration during primary percutaneous coronary intervention in cardiogenic shock complicating ST-segment elevation myocardial infarction. *Cardiovasc Revasc Med* 2013;**14**:307–10. http://dx.doi.org/10.1016/j.carrev.2013.08.006

25. Kumbhani DJ, Bavry AA, Desai MY, Bangalore S, Bhatt DL. Role of aspiration and mechanical thrombectomy in patients with acute myocardial infarction undergoing primary angioplasty: an updated meta-analysis of randomized trials. *J Am Coll Cardiol* 2013;**62**:1409–18. http://dx.doi.org/10.1016/j.jacc.2013.04.025

26. De Luca G, Navarese EP, Suryapranata H. A meta-analytic overview of thrombectomy during primary angioplasty. *Int J Cardiol* 2013;**166**:606–12. http://dx.doi.org/10.1016/j.ijcard.2011.11.102

27. Jolly SS, Cairns J, Yusuf S, Meeks B, Shestakovska O, Thabane L, *et al.* Design and rationale of the TOTAL trial: a randomized trial of routine aspiration thrombectomy with percutaneous coronary intervention (PCI) versus PCI alone in patients with ST-elevation myocardial infarction undergoing primary PCI. *Am Heart J* 2014;**167**:315–21.e1. http://dx.doi.org/10.1016/j.ahj.2013.12.002

28. Thiele H, Schindler K, Friedenberger J, Eitel I, Fürnau G, Grebe E, *et al.* Intracoronary compared with intravenous bolus abciximab application in patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention: the randomized Leipzig immediate percutaneous coronary intervention abciximab IV versus IC in ST-elevation myocardial infarction trial. *Circulation* 2008;**118**:49–57. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.747642

29. Bartorelli AL, Trabattoni D, Galli S, Grancini L, Cozzi S, Ravagnani P. Successful dissolution of occlusive coronary thrombus with local administration of abciximab during PTCA. *Catheter Cardiovasc Interv* 1999;**48**:211–13. http://dx.doi.org/10.1002/(SICI)1522-726X(199910)48:2<211::AID-CCD20>3.0.CO;2-V

30. Kakkar AK, Moustapha A, Hanley HG, Weiss M, Caldito G, Misra P, *et al.* Comparison of intracoronary vs. intravenous administration of abciximab in coronary stenting. *Catheter Cardiovasc Interv* 2004;**61**:31–4. http://dx.doi.org/10.1002/ccd.10730

31. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, *et al.* Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;**355**:2203–16. http://dx.doi.org/10.1056/NEJMoa062437

32. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, *et al.* Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;**358**:2218–30. http://dx.doi.org/10.1056/NEJMoa0708191

33. Ishihara M, Sato H, Tateishi H, Kawagoe T, Shimatani Y, Kurisu S, *et al.* Attenuation of the no-reflow phenomenon after coronary angioplasty for acute myocardial infarction with intracoronary papaverine. *Am Heart J* 1996;**132**:959–63. http://dx.doi.org/10.1016/S0002-8703(96)90005-8

34. Kaplan BM, Benzuly KH, Kinn JW, Bowers TR, Tilli FV, Grines CL, *et al.* Treatment of no-reflow in degenerated saphenous vein graft interventions: comparison of intracoronary verapamil and nitroglycerin. *Cathet Cardiovasc Diagn* 1996;**39**:113–18. http://dx.doi.org/10.1002/(SICI)1097-0304(199610)39:2<113::AID-CCD1>3.0.CO;2-I

35. Kloner RA, Alker KJ. The effect of streptokinase on intramyocardial hemorrhage, infarct size, and the no-reflow phenomenon during coronary reperfusion. *Circulation* 1984;**70**:513–21. http://dx.doi.org/10.1161/01.CIR.70.3.513

36. Werner GS, Lang K, Kuehnert H, Figulla HR. Intracoronary verapamil for reversal of no-reflow during coronary angioplasty for acute myocardial infarction. *Catheter Cardiovasc Interv* 2002;**57**:444–51. http://dx.doi.org/10.1002/ccd.10375

37. Weyrens FJ, Mooney J, Lesser J, Mooney MR. Intracoronary diltiazem for microvascular spasm after interventional therapy. *Am J Cardiol* 1995;**75**:849–50. http://dx.doi.org/10.1016/S0002-9149(99)80430-5

38. Rawitscher D, Levin TN, Cohen I, Feldman T. Rapid reversal of no-reflow using abciximab after coronary device intervention. *Cathet Cardiovasc Diagn* 1997;**42**:187–90. http://dx.doi.org/10.1002/(SICI)1097-0304(199710)42:2<187::AID-CCD20>3.0.CO;2-K

39. Skelding KA, Goldstein JA, Mehta L, Pica MC, O'Neill WW. Resolution of refractory no-reflow with intracoronary epinephrine. *Catheter Cardiovasc Interv* 2002;**57**:305–9. http://dx.doi.org/10.1002/ccd.10303

40. Ota S, Nishikawa H, Takeuchi M, Nakajima K, Nakamura T, Okamoto S, *et al.* Impact of nicorandil to prevent reperfusion injury in patients with acute myocardial infarction: Sigmart Multicenter Angioplasty Revascularization Trial (SMART). *Circ J* 2006;**70**:1099–104. http://dx.doi.org/10.1253/circj.70.1099

41. Kunadian V, Zorkun C, Williams SP, Biller LH, Palmer AM, Ogando KJ, *et al.* Intracoronary pharmacotherapy in the management of coronary microvascular dysfunction. *J Thromb Thrombolysis* 2008;**26**:234–42. http://dx.doi.org/10.1007/s11239-008-0276-0

42. Amit G, Cafri C, Yaroslavtsev S, Fuchs S, Paltiel O, Abu-Ful A, *et al.* Intracoronary nitroprusside for the prevention of the no-reflow phenomenon after primary percutaneous coronary intervention in acute myocardial infarction. A randomized, double-blind, placebo-controlled clinical trial. *Am Heart J* 2006;**152**:887.e9–14. http://dx.doi.org/10.1016/j.ahj.2006.05.010

43. Kobatake R, Sato T, Fujiwara Y, Sunami H, Yoshioka R, Ikeda T, *et al.* Comparison of the effects of nitroprusside versus nicorandil on the slow/no-reflow phenomenon during coronary interventions for acute myocardial infarction. *Heart Vessels* 2011;**26**:379–84. http://dx.doi.org/10.1007/s00380-010-0065-5

44. Niccoli G, Rigattieri S, De Vita MR, Valgimigli M, Corvo P, Fabbiocchi F, *et al.* Open-label, randomized, placebo-controlled evaluation of intracoronary adenosine or nitroprusside after thrombus aspiration during primary percutaneous coronary intervention for the prevention of microvascular obstruction in acute myocardial infarction: the REOPEN-AMI study (Intracoronary Nitroprusside Versus Adenosine in Acute Myocardial Infarction). *JACC Cardiovasc Interv* 2013;**6**:580–9. http://dx.doi.org/10.1016/j.jcin.2013.02.009

45. Parikh KH, Chag MC, Shah KJ, Shah UG, Baxi HA, Chandarana AH, *et al.* Intracoronary boluses of adenosine and sodium nitroprusside in combination reverses slow/no-reflow during angioplasty: a clinical scenario of ischemic preconditioning. *Can J Physiol Pharmacol* 2007;**85**:476–82. http://dx.doi.org/10.1139/Y07-013

46. Pasceri V, Pristipino C, Pelliccia F, Granatelli A, Speciale G, Roncella A, *et al.* Effects of the nitric oxide donor nitroprusside on no-reflow phenomenon during coronary interventions for acute myocardial infarction. *Am J Cardiol* 2005;**95**:1358–61. http://dx.doi.org/10.1016/j.amjcard.2005.01.082

47. Shinozaki N, Ichinose H, Yahikozawa K, Shimada H, Hoshino K. Selective intracoronary administration of nitroprusside before balloon dilatation prevents slow reflow during percutaneous coronary intervention in patients with acute myocardial infarction. *Int Heart J* 2007;**48**:423–33. http://dx.doi.org/10.1536/ihj.48.423

48. Wang HJ, Lo PH, Lin JJ, Lee H, Hung JS. Treatment of slow/no-reflow phenomenon with intracoronary nitroprusside injection in primary coronary intervention for acute myocardial infarction. *Catheter Cardiovasc Interv* 2004;**63**:171–6. http://dx.doi.org/10.1002/ccd.20149

49. Youssef AA, Wu CJ, Hang CL, Cheng CI, Yang CH, Chen CJ, *et al.* Impact of percusurge device conjugative with intracoronary administration of nitroprusside on no-reflow phenomenon following primary percutaneous coronary intervention. *Circ J* 2006;**70**:1538–42. http://dx.doi.org/10.1253/circj.70.1538

50. Claeys MJ, Bosmans J, De Ceuninck M, Beunis A, Vergauwen W, Vorlat A, *et al.* Effect of intracoronary adenosine infusion during coronary intervention on myocardial reperfusion injury in patients with acute myocardial infarction. *Am J Cardiol* 2004;**94**:9–13. http://dx.doi.org/10.1016/j.amjcard.2004.03.021

51. Desmet W, Bogaert J, Dubois C, Sinnaeve P, Adriaenssens T, Pappas C, *et al.* High-dose intracoronary adenosine for myocardial salvage in patients with acute ST-segment elevation myocardial infarction. *Eur Heart J* 2011;**32**:867–77. http://dx.doi.org/10.1093/eurheartj/ehq492

52. Fokkema ML, Vlaar PJ, Vogelzang M, Gu YL, Kampinga MA, de Smet BJ, *et al.* Effect of high-dose intracoronary adenosine administration during primary percutaneous coronary intervention in acute myocardial infarction: a randomized controlled trial. *Circ Cardiovasc Interv* 2009;**2**:323–9. http://dx.doi.org/10.1161/CIRCINTERVENTIONS.109.858977.109.858977

53. Grygier M, Araszkiewicz A, Lesiak M, Janus M, Kowal J, Skorupski W, *et al.* New method of intracoronary adenosine injection to prevent microvascular reperfusion injury in patients with acute myocardial infarction undergoing percutaneous coronary intervention. *Am J Cardiol* 2011;**107**:1131–5. http://dx.doi.org/10.1016/j.amjcard.2010.12.010

54. Mahaffey KW, Puma JA, Barbagelata NA, DiCarli MF, Leesar MA, Browne KF, *et al.* Adenosine as an adjunct to thrombolytic therapy for acute myocardial infarction: results of a multicenter, randomized, placebo-controlled trial: the Acute Myocardial Infarction STudy of ADenosine (AMISTAD) trial. *J Am Coll Cardiol* 1999;**34**:1711–1720. http://dx.doi.org/10.1016/S0735-1097(99)00418-0

55. Marzilli M, Orsini E, Marraccini P, Testa R. Beneficial effects of intracoronary adenosine as an adjunct to primary angioplasty in acute myocardial infarction. *Circulation* 2000;**101**:2154–9. http://dx.doi.org/10.1161/01.CIR.101.18.2154

56. Micari A, Belcik TA, Balcells EA, Powers E, Wei K, Kaul S, *et al.* Improvement in microvascular reflow and reduction of infarct size with adenosine in patients undergoing primary coronary stenting. *Am J Cardiol* 2005;**96**:1410–15. http://dx.doi.org/10.1016/j.amjcard.2005.06.090

57. Petronio AS, De Carlo M, Ciabatti N, Amoroso G, Limbruno U, Palagi C, *et al.* Left ventricular remodeling after primary coronary angioplasty in patients treated with abciximab or intracoronary adenosine. *Am Heart J* 2005;**150**:1015. http://dx.doi.org/10.1016/j.ahj.2005.07.012

58. Quintana M, Hjemdahl P, Sollevi A, Kahan T, Edner M, Rehnqvist N, *et al.* Left ventricular function and cardiovascular events following adjuvant therapy with adenosine in acute myocardial infarction treated with thrombolysis, results of the ATTenuation by Adenosine of Cardiac Complications (ATTACC) study. *Eur J Clin Pharmacol* 2003;**59**:1–9.

59. Ross AM, Gibbons RJ, Stone GW, Kloner RA, Alexander RW. A randomized, double-blinded, placebo-controlled multicenter trial of adenosine as an adjunct to reperfusion in the treatment of acute myocardial infarction (AMISTAD-II). *J Am Coll Cardiol* 2005;**45**:1775–80. http://dx.doi.org/10.1016/j.jacc.2005.02.061

60. Stoel MG, Marques KM, de Cock CC, Bronzwaer JG, von Birgelen C, Zijlstra F. High dose adenosine for suboptimal myocardial reperfusion after primary PCI: a randomized placebo-controlled pilot study. *Catheter Cardiovasc Interv* 2008;**71**:283–9. http://dx.doi.org/10.1002/ccd.21334

61. Zhang H, Tian NL, Hu ZY, Wang F, Chen L, Zhang YJ, *et al.* Three hours continuous injection of adenosine improved left ventricular function and infarct size in patients with ST-segment elevation myocardial infarction. *Chin Med J* 2012;**125**:1713–19.

62. Vijayalakshmi K, Whittaker VJ, Kunadian B, Graham J, Wright RA, Hall JA, *et al.* Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. *Heart* 2006;**92**:1278–84. http://dx.doi.org/10.1136/hrt.2005.075077

63. Berne RM. The role of adenosine in the regulation of coronary blood flow. *Circ Res* 1980;**47**:807–13. http://dx.doi.org/10.1161/01.RES.47.6.807

64. Ernst PB, Garrison JC, Thompson LF. Much ado about adenosine: adenosine synthesis and function in regulatory T cell biology. *J Immunol* 2010;**185**:1993–8. http://dx.doi.org/10.4049/jimmunol.1000108

65. Linden J. Molecular approach to adenosine receptors: receptor-mediated mechanisms of tissue protection. *Ann Rev Pharmacol Toxicol* 2001;**41**:775–87. http://dx.doi.org/10.1146/annurev.pharmtox.41.1.775

66. Olafsson B, Forman MB, Puett DW, Pou A, Cates CU, Friesinger GC, *et al.* Reduction of reperfusion injury in the canine preparation by intracoronary adenosine: importance of the endothelium and the no-reflow phenomenon. *Circulation* 1987;**76**:1135–45. http://dx.doi.org/10.1161/01.CIR.76.5.1135

67. Bates JN, Baker MT, Guerra R Jr, Harrison DG. Nitric oxide generation from nitroprusside by vascular tissue. Evidence that reduction of the nitroprusside anion and cyanide loss are required. *Biochem Pharmacol* 1991;**42**:S157–65. http://dx.doi.org/10.1016/0006-2952(91)90406-U

68. Gavin JB, Maxwell L, Edgar SG. Microvascular involvement in cardiac pathology. *J Mol Cell Cardiol* 1998;**30**:2531–40. http://dx.doi.org/10.1006/jmcc.1998.0824

69. Pemberton M, Anderson GL, Barker JH. Characterization of microvascular vasoconstriction following ischemia/reperfusion in skeletal muscle using videomicroscopy. *Microsurgery* 1996;**17**:9–16. http://dx.doi.org/10.1002/(SICI)1098-2752(1996)17:1<9::AID-MICR2>3.0.CO;2-K

70. Wang WZ, Anderson G, Fleming JT, Peter FW, Franken RJ, Acland RD, *et al.* Lack of nitric oxide contributes to vasospasm during ischemia/reperfusion injury. *Plast Reconstructr Surg* 1997;**99**:1099–108. http://dx.doi.org/10.1097/00006534-199704000-00028

71. Kloner RA, Forman MB, Gibbons RJ, Ross AM, Alexander RW, Stone GW. Impact of time to therapy and reperfusion modality on the efficacy of adenosine in acute myocardial infarction: the AMISTAD-2 trial. *Eur Heart J* 2006;**27**:2400–5. http://dx.doi.org/10.1093/eurheartj/ehl094

72. Masci PG, Ganame J, Francone M, Desmet W, Lorenzoni V, Iacucci I, *et al.* Relationship between location and size of myocardial infarction and their reciprocal influences on post-infarction left ventricular remodelling. *Eur Heart J* 2011;**32**:1640–8. http://dx.doi.org/10.1093/eurheartj/ehr064

73. Aung Naing K, Li L, Su Q, Wu T. Adenosine and verapamil for no-reflow during primary percutaneous coronary intervention in people with acute myocardial infarction. *Cochrane Database Syst Rev* 2013;**6**:CD009503. http://dx.doi.org/10.1002/14651858.cd009503.pub2

74. Nazir SA, Khan JN, Mahmoud IZ, Greenwood JP, Blackman DJ, Kunadian V, *et al.* 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 randomised controlled trial. *Trials* 2014;**15**:371. http://dx.doi.org/10.1186/1745-6215-15-371

75. Kelly DJ, McCann GP, Blackman D, Curzen NP, Dalby M, Greenwood JP, *et al.* Complete Versus culprit-Lesion only PRimary PCI Trial (CVLPRIT): a multicentre trial testing management strategies when multivessel disease is detected at the time of primary PCI: rationale and design. *Eurointervention* 2013;**8**:1190–8. http://dx.doi.org/10.4244/EIJV8I10A183

76. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, *et al.* Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med* 2013;**368**:1379–87. http://dx.doi.org/10.1056/NEJMoa1301092

77. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, *et al.* Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–15. http://dx.doi.org/10.1056/NEJMoa0706482

78. National Institute for Health and Care Excellence. *Prasugrel for the Treatment of Acute Coronary Syndromes with Percutaneous Coronary Intervention. NICE Technology Appraisal Guidance TA182*. London: NICE; 2009. URL: www.nice.org.uk/nicemedia/live/12028/45321/45321.pdf (accessed 15 January 2014).

79. James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, *et al.* Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. *Am Heart J* 2009;**157**:599–605. http://dx.doi.org/10.1016/j.ahj.2009.01.003

80. European Society of Cardiology. *ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation*. 2012. URL: www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/Guidelines_AMI_STEMI.pdf (accessed 15 January 2014).

81. National Institute for Health and Care Excellence. *Ticagrelor for the Treatment of Acute Coronary Syndromes*. NICE technology appraisal guidance TA236. London: NICE; 2011. URL: www.nice.org.uk/nicemedia/live/13588/56819/56819.pdf (accessed 15 January 2014).

82. Shahzad A, Kemp I, Mars C, Wilson K, Roome C, Cooper R, *et al.* Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014;**384**:1849–58. http://dx.doi.org/10.1016/S0140-6736(14)60924-7

83. Schroder R, Dissmann R, Bruggemann T, Wegscheider K, Linderer T, Tebbe U, *et al.* Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. *J Am Coll Cardiol* 1994;**24**:384–91. http://dx.doi.org/10.1016/0735-1097(94)90292-5

84. Gibson CM, Cannon CP, Murphy SA, Ryan KA, Mesley R, Marble SJ, *et al.* Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000;**101**:125–30. http://dx.doi.org/10.1161/01.CIR.101.2.125

85. Gibson CM, Cannon CP, Murphy SA, Marble SJ, Barron HV, Braunwald E, *et al.* Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. *Circulation* 2002;**105**:1909–13. http://dx.doi.org/10.1161/01.CIR.0000014683.52177.B5

86. Vogelzang M, Vlaar PJ, Svilaas T, Amo D, Nijsten MW, Zijlstra F. Computer-assisted myocardial blush quantification after percutaneous coronary angioplasty for acute myocardial infarction: a substudy from the TAPAS trial. *Eur Heart J* 2009;**30**:594–9. http://dx.doi.org/10.1093/eurheartj/ehn542

87. Gibson CM, Cannon CP, Daley WL, Dodge JT Jr, Alexander B Jr, Marble SJ, *et al.* TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 1996;**93**:879–88. http://dx.doi.org/10.1161/01.CIR.93.5.879

88. Kunadian V, Harrigan C, Zorkun C, Palmer AM, Ogando KJ, Biller LH, *et al.* Use of the TIMI frame count in the assessment of coronary artery blood flow and microvascular function over the past 15 years. *J Thromb Thrombolysis* 2009;**27**:316–28. http://dx.doi.org/10.1007/s11239-008-0220-3

89. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI study group. *N Engl J Med* 1985;**312**:932–6. http://dx.doi.org/10.1056/NEJM198504043121435

90. Gibson CM, de Lemos JA, Murphy SA, Marble SJ, McCabe CH, Cannon CP, *et al.* Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. *Circulation* 2001;**103**:2550–4. http://dx.doi.org/10.1161/01.CIR.103.21.2550

91. van't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. *Circulation* 1998;**97**:2302–6. http://dx.doi.org/10.1161/01.CIR.97.23.2302

92. Yuval R, Halon DA, Merdler A, Khader N, Karkabi B, Uziel K, *et al.* Patient comprehension and reaction to participating in a double-blind randomized clinical trial (ISIS-4) in acute myocardial infarction. *Arch Intern Med* 2000;**160**:1142–6. http://dx.doi.org/10.1001/archinte.160.8.1142

93. Williams BF, French JK, White HD, HERO-2 consent substudy investigators. Informed consent during the clinical emergency of acute myocardial infarction (HERO-2 consent substudy): a prospective observational study. *Lancet* 2003;**361**:918–22. http://dx.doi.org/10.1016/S0140-6736(03)12773-0

94. Ibrahim T, Hackl T, Nekolla SG, Breuer M, Feldmair M, Schömig A. Acute myocardial infarction: serial cardiac MR imaging shows a decrease in delayed enhancement of the myocardium during the 1st week after reperfusion. *Radiology* 2010;**254**:88–97. http://dx.doi.org/10.1148/radiol.09090660

95. Albert TSE, Kim RJ, Judd RM. Assessment of no-reflow regions using cardiac MRI. *Basic Res Cardiol* 2006;**101**:383–90. http://dx.doi.org/10.1007/s00395-006-0617-0

96. Tilak GS, Hsu LY, Hoyt RF Jr, Arai AE, Aletras AH. In vivo T2-weighted magnetic resonance imaging can accurately determine the ischemic area at risk for 2-day-old nonreperfused myocardial infarction. *Invest Radiol* 2008;**43**:7–15. http://dx.doi.org/10.1097/RLI.0b013e3181558822

97. Flett AS, Hasleton J, Cook C, Hausenloy D, Quarta G, Ariti C, *et al.* Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2011;**4**:150–6. http://dx.doi.org/10.1016/j.jcmg.2010.11.015

98. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, *et al.* Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–67. http://dx.doi.org/10.1093/eurheartj/ehs184

99. Reed MD, Bell D. Clinical pharmacology of bivalirudin. *Pharmacotherapy* 2002;**22**:105S–11S. http://dx.doi.org/10.1592/phco.22.10.105S.33616

100. Cortese B, Picchi A, Micheli A, Limbruno U. Intracoronary bivalirudin for no reflow reversal: a second chance to treat this disorder? *J Thromb Thrombolysis* 2009;**28**:74–6. http://dx.doi.org/10.1007/s11239-008-0243-9

101. Bertomeu-Gonzalez V, Bodi V, Sanchis J, Nunez J, Lopez-Lereu MP, Pena G, *et al.* [Limitations of myocardial blush grade in the evaluation of myocardial perfusion in patients with acute myocardial infarction and TIMI grade 3 flow.] *Rev Esp Cardiol* 2006;**59**:575–81. http://dx.doi.org/10.1016/s1885-5857(07)60008-5

102. Bello D, Einhorn A, Kaushal R, Kenchaiah S, Raney A, Fieno D, *et al.* Cardiac magnetic resonance imaging: infarct size is an independent predictor of mortality in patients with coronary artery disease. *Magn Reson Imaging* 2011;**29**:50–6. http://dx.doi.org/10.1016/j.mri.2010.03.031

103. Eitel I, Desch S, de Waha S, Fuernau G, Gutberlet M, Schuler G, *et al.* Long-term prognostic value of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. *Heart* 2011;**97**:2038–45. http://dx.doi.org/10.1136/heartjnl-2011-300098

104. Ezekowitz JA, Armstrong PW, Granger CB, Theroux P, Stebbins A, Kim RJ, *et al.* Predicting chronic left ventricular dysfunction 90 days after ST-segment elevation myocardial infarction: an assessment of pexelizumab in acute myocardial infarction (APEX-AMI) substudy. *Am Heart J* 2010;**160**:272–8. http://dx.doi.org/10.1016/j.ahj.2010.05.035

105. Ganame J, Messalli G, Dymarkowski S, Rademakers FE, Desmet W, Van de Werf F, *et al.* Impact of myocardial haemorrhage on left ventricular function and remodelling in patients with reperfused acute myocardial infarction. *Eur Heart J* 2009;**30**:1440–9. http://dx.doi.org/10.1093/eurheartj/ehp093

106. Gerber BL. Accuracy of contrast-enhanced magnetic resonance imaging in predicting improvement of regional myocardial function in patients after acute myocardial infarction. *Circulation* 2002;**106**:1083–9. http://dx.doi.org/10.1161/01.CIR.0000027818.15792.1E

107. Kelle S, Roes SD, Klein C, Kokocinski T, de Roos A, Fleck E, *et al.* Prognostic value of myocardial infarct size and contractile reserve using magnetic resonance imaging. *J Am Coll Cardiol* 2009;**54**:1770–7. http://dx.doi.org/10.1016/j.jacc.2009.07.027

108. Klem I, Shah DJ, White RD, Pennell DJ, van Rossum AC, Regenfus M, *et al.* Prognostic value of routine cardiac magnetic resonance assessment of left ventricular ejection fraction and myocardial damage: an international, multicenter study. *Circ Cardiovasc Imaging* 2011;**4**:610–19. http://dx.doi.org/10.1161/CIRCIMAGING.111.964965

109. Kwong RY, Chan AK, Brown KA, Chan CW, Reynolds HG, Tsang S, *et al.* Impact of unrecognized myocardial scar detected by cardiac magnetic resonance imaging on event-free survival in patients presenting with signs or symptoms of coronary artery disease. *Circulation* 2006;**113**:2733–43. http://dx.doi.org/10.1161/CIRCULATIONAHA.105.570648

110. Larose E, Rodes-Cabau J, Pibarot P, Rinfret S, Proulx G, Nguyen CM, *et al.* Predicting late myocardial recovery and outcomes in the early hours of ST-segment elevation myocardial infarction traditional measures compared with microvascular obstruction, salvaged myocardium, and necrosis characteristics by cardiovascular magnetic resonance. *J Am Coll Cardiol* 2010;**55**:2459–69. http://dx.doi.org/10.1016/j.jacc.2010.02.033

111. Lund GK, Stork A, Muellerleile K, Bansmann MP, Schlichting U, Mu M, *et al.* Prediction of left ventricular remodeling and analysis of infarct resorption in patients with reperfused myocardial infarcts by using contrast-enhanced MR imaging. *Radiology* 2007;**245**:95–104. http://dx.doi.org/10.1148/radiol.2451061219

112. Wu E, Ortiz JT, Tejedor P, Lee DC, Kansal P, Carr JC, *et al.* Infarct size by contrast enhanced cardiac magnetic resonance is a stronger predictor of outcomes than left ventricular ejection fraction or end-systolic volume index: prospective cohort study. *Heart* 2008;**94**:730–6. http://dx.doi.org/10.1136/hrt.2007.122622

113. Lonborg J, Vejlstrup N, Kelbaek H, Holmvang L, Jorgensen E, Helqvist S, *et al.* Final infarct size measured by cardiovascular magnetic resonance in patients with ST elevation myocardial infarction predicts long-term clinical outcome: an observational study. *Eur Heart J Cardiovasc Imaging* 2013;**14**:387–95. http://dx.doi.org/10.1093/ehjci/jes271

114. Izquierdo M, Ruiz-Granell R, Bonanad C, Chaustre F, Gomez C, Ferrero A, *et al.* Value of early cardiovascular magnetic resonance for the prediction of adverse arrhythmic cardiac events after a first noncomplicated ST-segment-elevation myocardial infarction. *Circ Cardiovasc Imaging* 2013;**6**:755–61. http://dx.doi.org/10.1161/CIRCIMAGING.113.000702

115. Rahimi K, Banning AP, Cheng ASH, Pegg TJ, Karamitsos TD, Channon KM, *et al.* Prognostic value of coronary revascularisation-related myocardial injury: a cardiac magnetic resonance imaging study. *Heart* 2009;**95**:1937–43. http://dx.doi.org/10.1136/hrt.2009.173302

116. Nijveldt R, Beek AM, Hofman MB, Umans VA, Algra PR, Spreeuwenberg MD, *et al.* Late gadolinium-enhanced cardiovascular magnetic resonance evaluation of infarct size and microvascular obstruction in optimally treated patients after acute myocardial infarction. *J Cardiovasc Magn Reson* 2007;**9**:765–70. http://dx.doi.org/10.1080/10976640701545008

117. Beek AM, Nijveldt R, van Rossum AC. Intramyocardial hemorrhage and microvascular obstruction after primary percutaneous coronary intervention. *Int J Cardiovasc Imaging* 2010;**26**:49–55. http://dx.doi.org/10.1007/s10554-009-9499-1

118. Masci PG, Ganame J, Strata E, Desmet W, Aquaro GD, Dymarkowski S, *et al.* Myocardial salvage by CMR correlates with LV remodeling and early ST-segment resolution in acute myocardial infarction. *JACC Cardiovasc Imaging* 2010;**3**:45–51. http://dx.doi.org/10.1016/j.jcmg.2009.06.016

119. Hahn J-Y, Song YB, Gwon H-C, Choe YH, Kim JH, Sung J, *et al.* Relation of left ventricular infarct transmurality and infarct size after primary percutaneous coronary angioplasty to time from symptom onset to balloon inflation. *Am J Cardiol* 2008;**102**:1163–9. http://dx.doi.org/10.1016/j.amjcard.2008.06.042

120. Nijveldt R, van der Vleuten PA, Hirsch A, Beek AM, Tio RA, Tijssen JGP, *et al.* Early electrocardiographic findings and MR imaging-verified microvascular injury and myocardial infarct size. *JACC Cardiovasc Imaging* 2009;**2**:1187–94. http://dx.doi.org/10.1016/j.jcmg.2009.06.008

121. Humphrey SM, Seelye RN, Gavin JB. The influence of adenosine on the no-reflow phenomenon in anoxic and ischaemic hearts. *Pathology* 1982;**14**:129–33. http://dx.doi.org/10.3109/00313028209061285

122. Cronstein BN, Levin RI, Belanoff J, Weissmann G, Hirschhorn R. Adenosine: an endogenous inhibitor of neutrophil-mediated injury to endothelial cells. *J Clin Invest* 1986;**78**:760–70. http://dx.doi.org/10.1172/JCI112638

123. Babbitt DG, Virmani R, Forman MB. Intracoronary adenosine administered after reperfusion limits vascular injury after prolonged ischemia in the canine model. *Circulation* 1989;**80**:1388–99. http://dx.doi.org/10.1161/01.CIR.80.5.1388

124. Gruber HE, Hoffer ME, McAllister DR, Laikind PK, Lane TA, Schmid-Schoenbein GW, *et al.* Increased adenosine concentration in blood from ischemic myocardium by aica riboside. Effects on flow, granulocytes, and injury. *Circulation* 1989;**80**:1400–11. http://dx.doi.org/10.1161/01.CIR.80.5.1400

125. Hanna GP, Yhip P, Fujise K, Schroth GW, Rosales OR, Anderson HV, *et al.* Intracoronary adenosine administered during rotational atherectomy of complex lesions in native coronary arteries reduces the incidence of no-reflow phenomenon. *Catheter Cardiovasc Interv* 1999;**48**:275–8. http://dx.doi.org/10.1002/(SICI)1522-726X(199911)48:3<275::AID-CCD8>3.0.CO;2-M

126. Barcin C, Denktas AE, Lennon RJ, Hammes L, Higano ST, Holmes DR Jr, *et al.* Comparison of combination therapy of adenosine and nitroprusside with adenosine alone in the treatment of angiographic no-reflow phenomenon. *Catheter Cardiovasc Interv* 2004;**61**:484–91. http://dx.doi.org/10.1002/ccd.20010

127. Hillegass WB, Dean NA, Liao L, Rhinehart RG, Myers PR. Treatment of no-reflow and impaired flow with the nitric oxide donor nitroprusside following percutaneous coronary interventions: initial human clinical experience. *J Am Coll Cardiol* 2001;**37**:1335–43. http://dx.doi.org/10.1016/S0735-1097(01)01138-X

128. Pan W, Wang LF, Yu JH, Fan Y, Yang SS, Zhou LJ, *et al.* Intracoronary nitroprusside in the prevention of the no-reflow phenomenon in acute myocardial infarction. *Chin Med J* 2009;**122**:2718–23.

129. Zhao YJ, Fu XH, Ma XX, Wang DY, Dong QL, Wang YB, *et al.* Intracoronary fixed dose of nitroprusside via thrombus aspiration catheter for the prevention of the no-reflow phenomenon following primary percutaneous coronary intervention in acute myocardial infarction. *Exp Ther Med* 2013;**6**:479–84. http://dx.doi.org/10.3892/etm.2013.1139

130. Rubio R, Berne RM, Katori M. Release of adenosine in reactive hyperemia of the dog heart. *Am J Physiol* 1969;**216**:56–62.

131. Payne AR, Casey M, McClure J, McGeoch R, Murphy A, Woodward R, *et al.* Bright-blood T2-weighted MRI has higher diagnostic accuracy than dark-blood short tau inversion recovery MRI for detection of acute myocardial infarction and for assessment of the ischemic area at risk and myocardial salvage. *Circ Cardiovasc Imaging* 2011;**4**:210–19. http://dx.doi.org/10.1161/CIRCIMAGING.110.960450

132. McCann GP, Khan JN, Greenwood JP, Nazir S, Dalby M, Curzen N, *et al.* Complete versus lesion-only primary PCI: the randomized cardiovascular MR CVLPRIT substudy. *J Am Coll Cardiol* 2015;**66**:2713–24. http://dx.doi.org/10.1016/j.jacc.2015.09.099

133. Siddiqi N, Neil C, Bruce M, MacLennan G, Cotton S, Papadopoulou S, *et al.* Intravenous sodium nitrite in acute ST-elevation myocardial infarction: a randomized controlled trial (NIAMI). *Eur Heart J* 2014;**35**:1255–62. http://dx.doi.org/10.1093/eurheartj/ehu096

134. Raman SV, Ambrosio G. T2-cardiac magnetic resonance: has Elvis left the building? *Circ Cardiovasc Imaging* 2011;**4**:198–200. http://dx.doi.org/10.1161/CIRCIMAGING.111.965343

135. Ferreira VM, Piechnik SK, Dall'Armellina E, Karamitsos TD, Francis JM, Choudhury RP, *et al.* Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2012;**14**:42. http://dx.doi.org/10.1186/1532-429X-14-42

136. Dall'Armellina E, Piechnik SK, Ferreira VM, Si QL, Robson MD, Francis JM, *et al.* Cardiovascular magnetic resonance by non contrast T1-mapping allows assessment of severity of injury in acute myocardial infarction. *J Cardiovasc Magn Reson* 2012;**14**:15. http://dx.doi.org/10.1186/1532-429X-14-15

137. Nazir SA, Khan JN, McCann GP. Free breathing motion-corrected T1 mapping for robust assessment of myocardial injury post myocardial infarction. *Int J Cardiovasc Imaging* 2015;**31**:123–4. http://dx.doi.org/10.1007/s10554-014-0500-2

Appendix 1 Main randomised controlled trials investigating the role of adenosine and sodium nitroprusside in attenuating or preventing microvascular obstruction in ST-elevation myocardial infarction treated with primary percutaneous coronary intervention

Study/author	Year	Main inclusion/exclusion	Number of patients (*n* given study drug/total *N*)	Age (years), mean; time to PPCI (minutes), median	Dose administered	Mode of drug delivery	Primary outcome(s)[a]	Secondary outcome(s)[a]	Main findings[a]	Main limitations
Adenosine										
Niccoli *et al.*[44]	2013	Symptom onset < 12 hours before enrolment; TFG 0–1 in IRA pre PCI; 'rescue' PCI; excluded LBBB	80/240	63; 278	120-µg rapid bolus then 2 mg over 2 minutes	Selective IC	STR > 70%	TFG; MBG; 30-day MACE	↑ STR; ↑ MBG; ↓ TFC	No direct assessment of IS/MVO
Zhang *et al.*[61]	2012	Symptom onset < 12 hours before enrolment; 'new' LBBB; TIMI 0–3; excluded MVD	59/90	63; 279	50 or 70 µg/kg/minute	i.v. infusion (3 hours)	IS (SPECT)	TFG; MBG; incidence NR; LV function; MACE at 6 months	↓ IS (at 6 months); ↑ MBG; ↓ NR	No CMR imaging – IS may be underestimated by SPECT; IS only in 60%; MSI not assessed; no reported use of TA or GPIIbIIIa inhibitors
Desmet *et al.*[51]	2011	Symptom onset < 12 hours before enrolment; 'new' LBBB; TFG 0–3	56/110	61; 215 (150–296) and 193 (150–305) for adenosine and placebo, respectively[b]	4 mg	Selective IC	MSI and MVO (CMR)	TFG; TFC; MBG; STR; 30-day and 1-year MACE	No benefit	No routine TA; no details on IS data; assessed 'early' rather than 'late' MVO; no stratified randomisation: more anterior MIs in adenosine arm and ↑ (almost double) spontaneous reperfusion rate in control arm
Grygier *et al.*[53]	2011	Symptom onset < 6 hours before enrolment; TFG 0–2	35/70	65; 249	LCA 2 mg; RCA 1 mg	IC via guide catheter	MBG; STR	TFG; TFC; 30-day MACE	↑ MBG; ↑ STR; ↓ MACE	No imaging assessment of IS; no routine TA
Fokemma *et al.*[52]	2009	Symptom onset < 12 hours before enrolment; TFG 0–3; included MVD	226/448	62; 180 (130–288) and 165 (125–255) for adenosine and placebo, respectively[b]	2 × 120 µg	IC via guide catheter	Residual STD	STR; MBG, TFG; IS (enzymatic); 30-day MACE	No benefit	No imaging assessment of IS; low drug dose injected proximally via guide catheter

Study/author	Year	Main inclusion/exclusion	Number of patients (*n* given study drug/total *N*)	Age (years), mean; time to PPCI (minutes), median	Dose administered	Mode of drug delivery	Primary outcome(s)[a]	Secondary outcome(s)[a]	Main findings[a]	Main limitations
Stoel *et al.*[60]	2008	STR < 70% and persistent ST ↑ post PPCI with TFG 2–3 and < 30% residual stenosis	27/49	67; 220	60 mg	Selective IC (over 5–10 minutes)	STR	TFC; MBG; 1-year MACE	↑ STR; ↑ MBG; ↓ TFC	Preselected patients with suboptimal reperfusion success; no imaging assessment of IS; no TA; shorter ischaemic time in adenosine arm; no ITT analysis reported
Micari *et al.*[56]	2005	Symptom onset < 6 hours before enrolment; excluded if previous MI	14/30	57; 292	50 or 70 µg/kg/minute	i.v. infusion (3 hours)	MSI	MBV in AAR	↑ MSI, ↑ MBV	IS and AAR assessed by MCE; no TA; low study numbers; used anterior MI patients from AMISTAD-II[59]
Petronio *et al.*[57]	2005	Symptom onset < 6 hours before enrolment; TFG 0–1; included MVD	30/90	59; 179	4 mg	Selective IC	LV remodelling (LVEDV ≥ 20% on echo) at 6 months	Angiographic NR; TFC; ΔLVEDV	Improved angiographic results but no ↓ prevalence of remodelling	No direct IS assessment; selection bias ('alternate' randomisation); allowed use of other vasoactive drugs if NR occurred
Marzilli *et al.*[55]	2000	Symptom onset < 3 hours before enrolment; TFG 0–2; included MVD	27/54	60; 116	4 mg	Selective IC	Feasibility; safety; TFG	LV function; in-hospital clinical events	Well tolerated, feasible; ↑ flow, ↑ ventricular function, ↓ incidence NR	As for ATTACC;[58] no outpatient follow-up

Study/author	Year	Main inclusion/exclusion	Number of patients (*n* given study drug/total *N*)	Age (years), mean; time to PPCI (minutes), median	Dose administered	Mode of drug delivery	Primary outcome(s)[a]	Secondary outcome(s)[a]	Main findings[a]	Main limitations
SNP										
Zhao *et al.*[129]	2013	Symptom onset < 12 hours before enrolment; TFG 0–2; age ≤ 75 years	80/162	63; 345	100-µg rapid bolus	Selective IC	TFC; MBG; STR > 70%	TFG; LVEF (echo); MACE at 6 months	↓ TFC; ↑ STR; ↑ MBG; ↑ LVEF	No imaging assessment of IS
Niccoli *et al.*[44]	2013	Symptom onset < 12 hours before enrolment; TFG 0–1; 'rescue' PCI; excluded LBBB	80/240	63; 278	60-µg rapid bolus then 100 µg over 2 minutes	Selective IC	STR > 70%	TFG; MBG; 30-day MACE	No benefit	*See above*; Low dose SNP; more anterior MIs in SNP arm; ECG surrogate for IS
Pan *et al.*[128]	2009	Symptom onset < 12 hours before enrolment; TFG 0–3	46/92	53; 492	100-µg bolus; repeated after 5 minutes if TFG < 3	Selective IC	TFG; TFC; MCE parameters	Plasma Hs-CRP and NT-proBNP; MACE at 6 months	↑ TFG; ↓ TFC; ↓ MACE; improved MCE parameters	No direct imaging assessment of IS/MSI; TA at operator discretion (63%)
Parikh *et al.*[45]	2007	High-risk ACS; TIMI 0–2	26/75	55; N/A	50-µg bolus SNP ± 12-µg bolus adenosine	IC via guide catheter	TFG; MBG (visual)	MACE at 6 months	Combination of adenosine + SNP ↑ TFG, ↑ MBG and ↓ MACE vs. adenosine alone	Included non-STEMI ACS patients; no 'SNP only' arm; fewer high-risk lesions and greater prevalence of triple-vessel disease (possible preconditioning effect) in combination arm
Amit *et al.*[42]	2006	Symptom onset < 12 hours before enrolment; TFG 0–2; excluded LBBB	48/98	62; 202 (146–311) and 240 (146–325) for SNP and placebo, respectively[b]	60 µg	Selective IC	TFC; STR > 70%	TFG; MBG; MACE (TLR, MI or death) at 6 months	No ↓ TFC or MBG but ↓ MACE	No IS assessment; underpowered; no TA; only 45% received GPIIbIIIa inhibitor

ACS, acute coronary syndrome; Hs-CRP, high-sensitivity C-reactive protein; IS, infarct size; i.v., intravenous; LBBB, left bundle branch block; LCA, left coronary artery; LVEDV, LV end-diastolic volume; MBV, myocardial blood volume; MVD, multivessel disease; N/A, not available; NR, no-reflow; STD, ST-segment deviation; TA, thrombus aspiration; TFC, TIMI frame count; TLR, target lesion revascularisations.

a STR defined as > 50% unless specifically stated.

b Median and IQR reported.

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