Clinical trial results:
Randomized Controlled Trial Comparing Intracoronary Administration of Adenosine or Sodium Nitroprusside to Control for Attenuation of Microvascular
Obstruction During Primary Percutaneous Coronary Intervention

Summary

EudraCT number	2010-023211-34
Trial protocol	GB
Global end of trial date	10 September 2014

Results information

Result version number	v1 (current)
This version publication date	03 April 2019
First version publication date	03 April 2019

Trial information

Trial identification

Sponsor protocol code	EDGE ID 11488 / CLRN 53469

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01747174
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals of Leicester NHS Trust
Sponsor organisation address	Trust HQ. Level 3. Balmoral Building. Leicester Royal Infirmary, Leicester, United Kingdom, LE1 5WW
Public contact	Professor Anthony Gershlick, University Hospitals of Leicester NHS Trust, agershlick@aol.com
Scientific contact	Professor Anthony Gershlick, University of Leicester, agershlick@aol.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal objective of our proposed study is to determine:-
1) Whether adjunctive medical treatment given via a very small tube (microcatheter) placed beyond the blockage downstream in the affected heart attack artery at the time of angioplasty for heart attack and following blood clot removal from the heart vessel, reduces downstream small blood vessel/microvascular obstruction (MVO) and heart muscle damage size (infarct size, IS) as determined by using cardiac magnetic resonance (CMR) scanners.
The principal study question is:
1) How might we attenuate small blood vessel obstruction and thus reduce heart attack size in patients undergoing angioplasty for heart attack?

Protection of trial subjects:

All patients received intravenous (IV) analgesia as required throughout the course of the treatment for their heart attack as part of standard therapy, pre-, peri- and post-procedure during which the blocked heart artery was re-opened using standard coronary angioplasty techniques.

Background therapy:

In all cases, PPCI was performed in line with accepted practice with trans-radial or femoral arterial access using 6-7 French size sheaths. Patients were pre-treated with dual antiplatelet therapy with aspirin (300mg loading dose and 75mg/day maintenance) and Prasugrel (60mg loading dose and 10mg/day maintenance) or Ticagrelor (loading dose 180mg and maintenance dose of 90mg twice daily) and given for up to 12 months. Bivalirudin, an anticoagulant agent, was administered to all patients (0.75 mg/Kg bolus plus infusion of 1.75 mg/Kg/hr) (as was regarded as standard practice then, in the absence of specific contraindication

Evidence for comparator:

Adenosine is a potent vasodilator of arterioles and has been shown to reduce adverse outcome and death in the setting of MVO. In experimental animal models, adenosine reduces ischaemia-reperfusion injury, limits IS, and improves ventricular function. Studies have reported lower MVO rates following IC adenosine boluses and reduced IS expressed as a percentage of the area at risk (AAR) following 3h IV adenosine infusion compared with placebo.

Sodium nitroprusside (SNP) is a direct nitric oxide (NO) donor demonstrated to have multiple vascular functions, including vasodilatation of arterioles, inhibition of platelet adhesion and anti-inflammatory activity. Local delivery of SNP is effective in reducing MVO in animal reperfusion-injury models. Furthermore, IC SNP appears to produce an equivalent but more prolonged coronary hyperaemia than adenosine. Studies have reported improved myocardial reperfusion with IC SNP.

Actual start date of recruitment	01 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 247
Worldwide total number of subjects	247
EEA total number of subjects	247

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	167
From 65 to 84 years	76
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

STEMI patients were enrolled between October 2011 and April 2014 in four regional cardiac centres in the UK.

Pre-assignment

Screening details:

All patients >18 years age, presenting within 6 hours of symptom onset of STEMI, with ST-segment elevation ≥2mm in ≥2 contiguous leads and with a baseline corrected QT interval (QTc) <450ms on admission ECG were eligible and assented.

Period 1

Period 1 title	Final enrolment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Following consent, patients were randomised 1:1:1 to: adjunctive IC adenosine, SNP or control (standard angioplasty alone), by a member of the research team, using a dedicated 24/7 computerised telephone service. All analyses were conducted blinded to patient details A clinical events committee, blinded to patient details and treatment allocation, reviewed and adjudicated key trial adverse events using original source documents.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard PCI + Intra-coronary (IC) Adenosine

Arm description:

Drug: IC Adenosine
IC Adenosine 1mg injected distally via micro-catheter in to infarct-related artery (IRA) following thrombus aspiration with further dose (1mg if IRA is right coronary artery otherwise 2mg) via guide catheter following coronary stent deployment.

Procedure: Standard PCI
PCI (angioplasty) procedure with thrombectomy (via aspiration catheter) and bivalirudin given as standard.

Arm type	Experimental
Investigational medicinal product name	Adenosine
Investigational medicinal product code	
Other name	Adenocor
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intracoronary use

Dosage and administration details:

Following manual thrombectomy and thorough flushing of the catheter, the first drug dose (adenosine 1 mg) was injected as distally as possible via the thrombus aspiration catheter. Immediately following stent deployment, and providing a repeat measure of QTc was <450ms and remained <60ms increased over the baseline value, the second drug dose (adenosine 1mg if IRA was the right coronary artery (RCA) otherwise 2mg) was given by slow injection (over 1 minute) via the guide catheter.

Arm title	Standard PCI + IC Sodium Nitroprusside (SNP)

Arm description:

Drug: IC Sodium nitroprusside (SNP)
IC SNP 250mcg injected distally via micro-catheter distally in to IRA following thrombus aspiration with further 250 mcg dose delivered via guide catheter following coronary stent deployment.

Procedure: Standard PCI
PCI procedure with thrombectomy (via aspiration catheter) and bivalirudin given as standard.

Arm type	Experimental
Investigational medicinal product name	Sodium nitroprusside
Investigational medicinal product code	
Other name	Sodium pentacyanonitrosylferrate(II), Sodium nitroferricyanide, Sodium pentacyanonitrosylferrate, SNP
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intracoronary use

Dosage and administration details:

Following manual thrombectomy and thorough flushing of the catheter, the first drug dose (SNP 250 mcg) was injected as distally as possible via the thrombus aspiration catheter. Immediately following stent deployment, and providing a repeat measure of QTc was <450ms and remained <60ms increased over the baseline value, the second drug dose (SNP 250 mcg) was given by slow injection (over 1 minute) via the guide catheter.

Arm title	Standard PCI

Arm description:

Procedure: Standard PCI
PCI procedure with thrombectomy (via aspiration catheter) and bivalirudin given as standard.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Standard PCI + Intra-coronary (IC) Adenosine	Standard PCI + IC Sodium Nitroprusside (SNP)	Standard PCI
Started	82	79	86
Completed	77	75	81
Not completed	5	4	5
Consent withdrawn by subject	4	3	5
Lost to follow-up	1	1	-

Baseline characteristics

Reporting groups

Reporting group title	Standard PCI + Intra-coronary (IC) Adenosine

Reporting group description:

Drug: IC Adenosine
IC Adenosine 1mg injected distally via micro-catheter in to infarct-related artery (IRA) following thrombus aspiration with further dose (1mg if IRA is right coronary artery otherwise 2mg) via guide catheter following coronary stent deployment.

Procedure: Standard PCI
PCI (angioplasty) procedure with thrombectomy (via aspiration catheter) and bivalirudin given as standard.

Reporting group title	Standard PCI + IC Sodium Nitroprusside (SNP)

Reporting group description:

Drug: IC Sodium nitroprusside (SNP)
IC SNP 250mcg injected distally via micro-catheter distally in to IRA following thrombus aspiration with further 250 mcg dose delivered via guide catheter following coronary stent deployment.

Procedure: Standard PCI
PCI procedure with thrombectomy (via aspiration catheter) and bivalirudin given as standard.

Reporting group title	Standard PCI

Reporting group description:

Procedure: Standard PCI
PCI procedure with thrombectomy (via aspiration catheter) and bivalirudin given as standard.

Reporting group values	Standard PCI + Intra-coronary (IC) Adenosine	Standard PCI + IC Sodium Nitroprusside (SNP)	Standard PCI
Number of subjects	82	79	86
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	57.9	60.5	59.5
standard deviation	± 12.8	± 13.0	± 11.2
Gender categorical Units: Subjects			
Female	17	13	22
Male	65	66	64

Reporting group values	Total		

Number of subjects	247		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	52		
Male	195		

End points

End points reporting groups

Reporting group title	Standard PCI + Intra-coronary (IC) Adenosine

Reporting group description:

Drug: IC Adenosine
IC Adenosine 1mg injected distally via micro-catheter in to infarct-related artery (IRA) following thrombus aspiration with further dose (1mg if IRA is right coronary artery otherwise 2mg) via guide catheter following coronary stent deployment.

Procedure: Standard PCI
PCI (angioplasty) procedure with thrombectomy (via aspiration catheter) and bivalirudin given as standard.

Reporting group title	Standard PCI + IC Sodium Nitroprusside (SNP)

Reporting group description:

Drug: IC Sodium nitroprusside (SNP)
IC SNP 250mcg injected distally via micro-catheter distally in to IRA following thrombus aspiration with further 250 mcg dose delivered via guide catheter following coronary stent deployment.

Procedure: Standard PCI
PCI procedure with thrombectomy (via aspiration catheter) and bivalirudin given as standard.

Reporting group title	Standard PCI

Reporting group description:

Procedure: Standard PCI
PCI procedure with thrombectomy (via aspiration catheter) and bivalirudin given as standard.

Primary: CMR-infarct size

End point title	CMR-infarct size

End point description:

CMR measured infarct size (determined from late-gadolinium enhanced CMR images) expressed as % of total left ventricular mass (determined by functional analysis of CMR cine images)

End point type	Primary

End point timeframe:

48-72 hours post-infarct

End point values	Standard PCI + Intra-coronary (IC) Adenosine	Standard PCI + IC Sodium Nitroprusside (SNP)	Standard PCI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	63	69	65	
Units: % Left ventricular Mass				
median (inter-quartile range (Q1-Q3))	10.1 (4.7 to 16.2)	10 (4.2 to 15.8)	8.3 (1.9 to 14)	

Statistical analyses

Statistical analysis title	Adenosine vs Control

Statistical analysis description:

Comparison of infarct size between patients receiving intra-coronary adenosine during angioplasty and control group (those who did not receive a study drug i.e. conventional primary angioplasty alone).

Comparison groups	Standard PCI + Intra-coronary (IC) Adenosine v Standard PCI
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.062
Method	t-test, 2-sided

Notes:

[1] - Comparison of infarct size between groups via independent t-test on log-transformed scale. Potential significant confounders of infarct size (age, sex, diabetes, anterior MI, ischaemia time and collateral blood flow to the infarct territory determined by the Rentrop score were adjusted for.

Statistical analysis title	SNP vs Control

Statistical analysis description:

Comparison of infarct size between patients receiving intra-coronary SNP during angioplasty and control group (those who did not receive a study drug i.e. conventional primary angioplasty alone).

Comparison groups	Standard PCI v Standard PCI + IC Sodium Nitroprusside (SNP)
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.16
Method	t-test, 2-sided

Notes:

[2] - Comparison of infarct size between groups via independent t-test on log-transformed scale. Potential significant confounders of infarct size (age, sex, diabetes, anterior MI, ischaemia time and collateral blood flow to the infarct territory determined by the Rentrop score were adjusted for.

Secondary: MACE

End point title	MACE

End point description:

Composite of death, stroke, re-infarction, heart failure and target lesion revascularisation

End point type	Secondary

End point timeframe:

Up to 6 months (180 days) follow-up from enrolment date (date of myocardial infarction)

End point values	Standard PCI + Intra-coronary (IC) Adenosine	Standard PCI + IC Sodium Nitroprusside (SNP)	Standard PCI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	79	86	
Units: Integers	12	5	2	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All patients were followed up for at least one month following randomisation and throughout the course of the study until the last patient recruited to the trial had completed one-month follow-up.

Adverse event reporting additional description:

Patients were contacted by telephone for follow-up at 6 months according to the study protocol. Unscheduled hospital admissions were also screened. Patients were additionally flagged with the Office for National Statistics to ensure mortality data was captured.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Frequency threshold for reporting non-serious adverse events: 1 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: all significant adverse events (serious and non-serious) are described in the publication of the main trial results, which has been attached to the record".

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2012	1) Addition of Ticagrelor as 2nd antiplatelet following publication of PLATO trial in line with ESC guidance. 2) Change of bleeding criteria from that used in HORIZONS-AMI to the TIMI criteria, due to the latter being most commonly used in interventional cardiology trials

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported