

**Clinical trial results:****Does nitrite reduce ischaemia-reperfusion injury in patients with acute ST segment elevation myocardial infarction?****Summary**

EudraCT number	2010-023571-26
Trial protocol	GB
Global end of trial date	04 February 2014

Results information

Result version number	v1 (current)
This version publication date	20 July 2018
First version publication date	20 July 2018
Summary attachment (see zip file)	NIAMI results paper (NIAMI results paper.pdf)

Trial information**Trial identification**

Sponsor protocol code	3/030/10
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Additional study identifiers

ISRCTN number	ISRCTN57596739
ClinicalTrials.gov id (NCT number)	NCT01388504
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Aberdeen
Sponsor organisation address	Foresterhill House Annex, Aberdeen, United Kingdom, AB25 2ZD
Public contact	Professor Graeme MacLennan, University of Aberdeen, 01224 438198, g.maclennan@abdn.ac.uk
Scientific contact	Professor Graeme MacLennan, University of Aberdeen, 01224 438198, g.maclennan@abdn.ac.uk
Sponsor organisation name	NHS Grampian
Sponsor organisation address	Foresterhill House Annexe, Aberdeen, United Kingdom, AB25 2ZD
Public contact	Professor Graeme MacLennan, University of Aberdeen, 01224 438198, g.maclennan@abdn.ac.uk
Scientific contact	Professor Graeme MacLennan, University of Aberdeen, 01224 438198, g.maclennan@abdn.ac.uk

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	03 June 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2013
Global end of trial reached?	Yes
Global end of trial date	04 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

In patients who have had a heart attack and are undergoing percutaneous coronary intervention (angioplasty), does a 5 minute intravenous injection of sodium nitrite immediately prior to opening of an infarct related artery reduce the size of the infarct (ie reduce the amount of damage caused to the heart)?

Protection of trial subjects:

Initial verbal agreement, followed by fully informed consent. Oversight by sponsor, data monitoring committee and trial steering committee who reviewed accruing data.

Background therapy:

All usual therapy. The protocol stated that unless absolutely indicated for the patient, IV or oral nitrates should not be commenced within five minutes of the percutaneous coronary intervention (PCI).

Evidence for comparator:

Placebo controlled (normal saline)

Actual start date of recruitment	11 August 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	Australia: 7
Country: Number of subjects enrolled	United Kingdom: 273
Worldwide total number of subjects	280
EEA total number of subjects	273

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)	148
From 65 to 84 years	119
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Patients presenting with acute STEMI were assessed for eligibility. A verbal statement was read to eligible patients and they were asked to give verbal agreement or informed consent. Those giving verbal agreement were approached post-intervention for fully informed consent.

Pre-assignment

Screening details:

Screening by medically qualified clinician against inclusion/exclusion criteria.

Period 1

Period 1 title	Recruitment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Sodium nitrite and placebo were identical in appearance, packaging and labelling.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sodium nitrite

Arm description:

sterile solution containing 70 micromol sodium nitrite dissolved in 5ml water injected intravenously over a period of 2½ - 5 minutes.

Arm type	Experimental
Investigational medicinal product name	Sodium Nitrite
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

sterile solution containing 70 micromol sodium nitrite dissolved in 5ml water injected intravenously over a period of 2½ - 5 minutes.

Arm title	Placebo
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Arm description:

sterile solution containing 0.9%w/v sodium chloride in 5ml water injected intravenously over a period of 2½ - 5 minutes.

Arm type	Placebo
Investigational medicinal product name	Normal saline (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

sterile solution containing 0.9%w/v sodium chloride in 5ml water injected intravenously over a period of 2½ - 5 minutes.

Number of subjects in period 1	Sodium nitrite	Placeo
Started	146	134
Completed	118	111
Not completed	28	23
No fully informed consent	15	-
Patient not eligible	-	15
Not eligible	13	-
No fully informed consent	-	8

Period 2

Period 2 title	confirmation of eligibility, consent
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sodium nitrite

Arm description:

sterile solution containing 70 micromol sodium nitrite dissolved in 5ml water injected intravenously over a period of 2½ - 5 minutes.

Arm type	Experimental
Investigational medicinal product name	Sodium Nitrite
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

sterile solution containing 70 micromol sodium nitrite dissolved in 5ml water injected intravenously over a period of 2½ - 5 minutes.

Arm title	Placeo
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Arm description:

sterile solution containing 0.9%w/v sodium chloride in 5ml water injected intravenously over a period of 2½ - 5 minutes.

Arm type	Placebo
Investigational medicinal product name	Normal saline (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

sterile solution containing 0.9%w/v sodium chloride in 5ml water injected intravenously over a period of 2½ - 5 minutes.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: trial in emergency setting. Period 1 was recruitment, period 2 confirmation of eligibility and consent, period 3 outcome assessment.

Number of subjects in period 2^[2]	Sodium nitrite	Placeo
Started	118	111
Completed	118	111

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Trial in emergency setting, not all people enrolled were confirmed as eligible after inclusion. Only those confirmed as eligible are in the baseline period.

Period 3

Period 3 title	Outcome assessment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sodium nitrite

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Sodium Nitrite
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

sterile solution containing 70 micromol sodium nitrite dissolved in 5ml water injected intravenously over a period of 2½ - 5 minutes.

Arm title	Placebo
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Arm description: -

Arm type	Placebo
Investigational medicinal product name	Normal saline (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

sterile solution containing 0.9%w/v sodium chloride in 5ml water injected intravenously over a period of 2½ - 5 minutes.

Number of subjects in period 3^[3]	Sodium nitrite	Placebo
	Started	85
Completed	85	88

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Some patients did not enter the outcome assessment phase.

Baseline characteristics

Reporting groups

Reporting group title	Sodium nitrite
Reporting group description: sterile solution containing 70 micromol sodium nitrite dissolved in 5ml water injected intravenously over a period of 2½ - 5 minutes.	
Reporting group title	Placeo
Reporting group description: sterile solution containing 0.9%w/v sodium chloride in 5ml water injected intravenously over a period of 2½ - 5 minutes.	

Reporting group values	Sodium nitrite	Placeo	Total
Number of subjects	118	111	229
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	63	64	
standard deviation	± 12	± 13	-
Gender categorical			
Units: Subjects			
Female	22	30	52
Male	96	81	177
Previous hypertension			
Units: Subjects			
Yes	35	35	70
No	83	76	159
Previous hyperlipidaemia			
Units: Subjects			
Yes	55	52	107
No	63	59	122
Previous diabetes			
Units: Subjects			
yes	14	19	33
No	104	92	196
Current smoker			
Units: Subjects			
Yes	53	47	100

No	65	64	129
Infarct site Units: Subjects			
Anterior	46	41	87
other	72	70	142
TIMI grade pre-PCI Units: Subjects			
TIMI0	105	101	206
TIMI1	11	9	20
missing	2	1	3
Nitrate use pre/during PCI Units: Subjects			
Yes	99	105	204
No	19	6	25
Morphine use pre/during PCI Units: Subjects			
Yes	70	66	136
No	48	45	93
Prior beta-blocker use Units: Subjects			
Yes	12	6	18
No	106	105	211
Prior calcium channel blocker use Units: Subjects			
Yes	24	29	53
No	94	82	176
Prior statin use Units: Subjects			
Yes	3	1	4
No	115	110	225
Prior heparin use Units: Subjects			
Yes	103	99	202
No	15	12	27
Prior ACE inhibitor use Units: Subjects			
Yes	0	1	1
No	118	110	228
Weight Units: kg			
median	82	77	
inter-quartile range (Q1-Q3)	75 to 91	69 to 89	-
BMI Units: kg/m ²			
arithmetic mean	28	27	
standard deviation	± 4	± 4	-
Syptom to balloon time Units: minutes			
arithmetic mean	208	238	
standard deviation	± 119	± 135	-
Symptom to balloon time			

Units: minutes			
median	164	203	
inter-quartile range (Q1-Q3)	127 to 256	133 to 317	-

End points

End points reporting groups

Reporting group title	Sodium nitrite
Reporting group description: sterile solution containing 70 micromol sodium nitrite dissolved in 5ml water injected intravenously over a period of 2½ - 5 minutes.	
Reporting group title	Placeo
Reporting group description: sterile solution containing 0.9%w/v sodium chloride in 5ml water injected intravenously over a period of 2½ - 5 minutes.	
Reporting group title	Sodium nitrite
Reporting group description: sterile solution containing 70 micromol sodium nitrite dissolved in 5ml water injected intravenously over a period of 2½ - 5 minutes.	
Reporting group title	Placeo
Reporting group description: sterile solution containing 0.9%w/v sodium chloride in 5ml water injected intravenously over a period of 2½ - 5 minutes.	
Reporting group title	Sodium nitrite
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Baseline characteristics
Subject analysis set type	Full analysis
Subject analysis set description: Received intervention/placebo, confirmed as eligible, provided fully informed consent	
Subject analysis set title	Outcome analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description: 173 participants who were recruited, confirmed as eligible and gave fully informed consent	

Primary: Infarct size 6-8 days

End point title	Infarct size 6-8 days
End point description:	
End point type	Primary
End point timeframe: 6-8 days	

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	88		
Units: Percent of LV myocardial mass				
arithmetic mean (standard deviation)	22.9 (± 13.5)	23.1 (± 13.2)		

Statistical analyses

Statistical analysis title	Infarct size 6-8 days
Comparison groups	Sodium nitrite v Placebo
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	0.7

Secondary: Troponin AUC

End point title	Troponin AUC
End point description:	
End point type	Secondary
End point timeframe:	
72 hours	

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	87		
Units: AUC				
arithmetic mean (standard deviation)	3734 (\pm 3091)	3807 (\pm 3262)		

Statistical analyses

Statistical analysis title	Troponin AUC
Comparison groups	Placebo v Sodium nitrite
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-125

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1139
upper limit	888

Secondary: Creatinine kinase

End point title	Creatinine kinase
End point description:	
End point type	Secondary
End point timeframe:	
72 hours	

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	87		
Units: AUC				
arithmetic mean (standard deviation)	67019 (\pm 42446)	59574 (\pm 48337)		

Statistical analyses

Statistical analysis title	Creatinine Kinase AUC
Comparison groups	Sodium nitrite v Placebo
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5766
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8695
upper limit	20288

Secondary: Infarct size measured using CMR LGE hyperenhancement extent defined using a cut-off of 5-SD greater than the intensity in the remote myocardium

End point title	Infarct size measured using CMR LGE hyperenhancement extent defined using a cut-off of 5-SD greater than the
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End point description:

End point type Secondary

End point timeframe:

6-8 days

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	84		
Units: infarct size				
arithmetic mean (standard deviation)	14.5 (\pm 10.5)	14.7 (\pm 11.2)		

Statistical analyses

Statistical analysis title	Infarct size 6-8 days (5-SD)
Comparison groups	Sodium nitrite v Placebo
Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	2.8

Secondary: final infarct size at 6 months

End point title final infarct size at 6 months

End point description:

End point type Secondary

End point timeframe:

6 months

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	55		
Units: infarct size				
arithmetic mean (standard deviation)	13.3 (± 8.7)	15.0 (± 9.7)		

Statistical analyses

Statistical analysis title	Final infarct size at 6 months
Comparison groups	Sodium nitrite v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	5.5

Secondary: Left Ventricular end diastolic volume 6-8 days

End point title	Left Ventricular end diastolic volume 6-8 days
End point description:	
End point type	Secondary
End point timeframe:	
6-8 days	

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	84		
Units: ml				
arithmetic mean (standard deviation)	159 (± 41)	162 (± 40)		

Statistical analyses

Statistical analysis title	Left Ventricular end diastolic volume 6-8 days
Comparison groups	Sodium nitrite v Placebo

Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.3
upper limit	9.2

Secondary: Left Ventricular end diastolic volume at 6 months

End point title	Left Ventricular end diastolic volume at 6 months
End point description:	
End point type	Secondary
End point timeframe:	
6 months	

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	54		
Units: ml				
arithmetic mean (standard deviation)	159 (\pm 42)	165 (\pm 37)		

Statistical analyses

Statistical analysis title	Left Ventricular end diastolic volume at 6 months
Comparison groups	Sodium nitrite v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.8
upper limit	9.8

Secondary: Left Ventricular end diastolic volume delta

End point title	Left Ventricular end diastolic volume delta
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End point description:

End point type	Secondary
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End point timeframe:

6-8 days to 6 months

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	51		
Units: ml				
arithmetic mean (standard deviation)	-1 (± 29)	-3 (± 32)		

Statistical analyses

Statistical analysis title	Left Ventricular end diastolic volume delta
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Comparison groups	Sodium nitrite v Placebo
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Number of subjects included in analysis	114
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.82
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Method	ANCOVA
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Parameter estimate	Mean difference (final values)
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Point estimate	1.3
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	-10.1
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upper limit	12.6
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Secondary: Left Ventricular end systolic volume

End point title	Left Ventricular end systolic volume
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End point description:

End point type	Secondary
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End point timeframe:

6-8 days

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	84		
Units: ml				
arithmetic mean (standard deviation)	85 (\pm 36)	85 (\pm 32)		

Statistical analyses

Statistical analysis title	Left Ventricular end systolic volume 6-8 days
Comparison groups	Sodium nitrite v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.93
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.4
upper limit	11.3

Secondary: Left Ventricular end systolic volume 6 months

End point title	Left Ventricular end systolic volume 6 months
End point description:	
End point type	Secondary
End point timeframe:	
6 months	

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	54		
Units: ml				
arithmetic mean (standard deviation)	75 (\pm 31)	78 (\pm 28)		

Statistical analyses

Statistical analysis title	Left Ventricular end systolic volume 6 months
Comparison groups	Sodium nitrite v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.7
upper limit	8.3

Secondary: Left Ventricular end systolic volume delta

End point title	Left Ventricular end systolic volume delta
End point description:	
End point type	Secondary
End point timeframe:	
6-8 days to 6 months	

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	63		
Units: ml				
arithmetic mean (standard deviation)	9 (± 25)	6 (± 24)		

Statistical analyses

Statistical analysis title	Left Ventricular end systolic volume delta
Comparison groups	Sodium nitrite v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	11.2

Secondary: Left ventricular ejection fraction

End point title	Left ventricular ejection fraction
End point description:	
End point type	Secondary
End point timeframe:	
6-8 days	

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	84		
Units: ml				
arithmetic mean (standard deviation)	48 (\pm 11)	50 (\pm 18)		

Statistical analyses

Statistical analysis title	Left ventricular ejection fraction 6-8 days
Comparison groups	Sodium nitrite v Placebo
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	2.4

Secondary: Left ventricular ejection fraction 6 months

End point title	Left ventricular ejection fraction 6 months
End point description:	

End point type	Secondary
End point timeframe:	
6 months	

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	54		
Units: ml				
arithmetic mean (standard deviation)	53 (± 9)	53 (± 9)		

Statistical analyses

Statistical analysis title	Left ventricular ejection fraction 6 months
Comparison groups	Sodium nitrite v Placebo
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	2.7

Secondary: Left ventricular ejection fraction delta

End point title	Left ventricular ejection fraction delta
End point description:	
End point type	Secondary
End point timeframe:	
6-8 days to 6 months	

End point values	Sodium nitrite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	51		
Units: ml				
arithmetic mean (standard deviation)	-5 (± 8)	-3 (± 22)		

Statistical analyses

Statistical analysis title	Left ventricular ejection fraction delta
Comparison groups	Placebo v Sodium nitrite
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	4.2

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

6 months post intervention

Assessment type	Systematic
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Dictionary used

Dictionary name	No dictionary used
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Dictionary version	0
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Reporting groups

Reporting group title	randomised - sodium nitrite
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Reporting group description: -

Reporting group title	randomised - placebo
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Reporting group description: -

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: Non-serious adverse events were not recorded in this study.

Serious adverse events	randomised - sodium nitrite	randomised - placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 146 (14.38%)	29 / 134 (21.64%)	
number of deaths (all causes)	1	4	
number of deaths resulting from adverse events	1	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign lung neoplasm			
subjects affected / exposed	0 / 146 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Procedural complication			
subjects affected / exposed	1 / 146 (0.68%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	1 / 146 (0.68%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Air embolism			

subjects affected / exposed	0 / 146 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
closure of patent foramen ovale			
subjects affected / exposed	0 / 146 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 146 (0.00%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 146 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 146 (0.68%)	4 / 134 (2.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	3 / 146 (2.05%)	4 / 134 (2.99%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 146 (0.68%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypotension			
subjects affected / exposed	2 / 146 (1.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			

subjects affected / exposed	0 / 146 (0.00%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Left ventricular thrombus			
subjects affected / exposed	1 / 146 (0.68%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 146 (1.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paroxysmal arrhythmia			
subjects affected / exposed	1 / 146 (0.68%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 146 (0.68%)	3 / 134 (2.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular failure			
subjects affected / exposed	0 / 146 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 146 (0.68%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	1 / 146 (0.68%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Chest pain			
subjects affected / exposed	1 / 146 (0.68%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 146 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Femoral artery pseudoaneurysm			
subjects affected / exposed	1 / 146 (0.68%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 146 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 146 (0.00%)	1 / 134 (0.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 146 (1.37%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			

subjects affected / exposed	1 / 146 (0.68%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	randomised - sodium nitrite	randomised - placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 146 (0.00%)	0 / 134 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 October 2010	<ol style="list-style-type: none">1. Change to when the primary outcome measure is assessed - final infarct size measured using MRI at six months (or slightly earlier for patients who may be scheduled for an implantable defibrillator/antiarrhythmic therapy). Oedema imaging (to correct for area at risk) will be added as a covariate to the analysis. The oedema imaging will be carried out during the first MRI scan that participants will have. Originally this was scheduled for 10-14 days after the MI, but we propose to carry this MRI out 6-8 days after the MI. The proposed changes to the timing of assessment of both final infarct size and oedema are based on the latest available evidence.2. Change in the timing of the secondary endpoints, previously assessed at MRI at 10-14 days, to MRI at 6-8 days. This change fits in with the change in time of the first MRI scan (described in 1 above), and avoids the need to have a third MRI scan at 10-14 days.3. Revision to inclusion criteria such that women aged <55 years who are not pregnant, sterilised, have had a hysterectomy or are using effective contraception, would be eligible to participate in the study.4. To clarify that patients with new left bundle branch block are suitable for inclusion in the study.5. To add an exclusion criteria (left Main disease which after PCI of their culprit lesion (culprit lesions may be located in the LAD or LCx or RCA) are likely to require CABG within the time course of the study period (6 months)).6. to reword the section on MRI imaging parameters. While the sequences will be standardised between centres as much as possible, but the individual scan parameters will be optimised as appropriate according to the individual patient. The parameters that were previously given in the protocol are one example of how the MRI might be carried out.7. To include three additional expected adverse events: pulmonary oedema, re-occlusion and respiratory arrest <p>(REC only)</p>

03 May 2011	<p>Inclusion of two additional exclusion criteria (prior coronary artery bypass grafting and prior thrombolysis for this event). Clarification that the prior revascularisation procedure is only an exclusion criteria if it was carried out in the same territory as the current infarct. Removal of atrial fibrillation at time of randomisation as an exclusion criterion.</p> <p>Restriction, unless absolutely indicated for the patient, the use of IV or oral nitrates within five minutes of PCI.</p> <p>Inclusion of additional outcome measure of LV end systolic volume index.</p> <p>Revision to the list of expected adverse events following administration of Investigational Medicinal Product or following PCI.</p> <p>Addition of information about storage conditions for IMP and placebo.</p> <p>Revision of dosing information such that the dose is given over 2.5 to 5 minutes.</p> <p>Revision of definition of PCI to include thrombus extraction.</p> <p>Confirmation that distilled water will be used for the preparation of IMP and placebo.</p> <p>Clarification of the timing of the injection in relation to the PCI.</p> <p>(REC only)</p>
18 August 2011	<p>Removal of requirement to gain consent from a relative/legal representative following verbal agreement from a trial participant who dies before giving informed consent.</p> <p>(REC only)</p>
22 February 2012	<p>To add an recruitment site outwith the UK. To clarify that part of the NIAMI project will be written up as an educational project.</p> <p>(REC only)</p>
06 August 2012	<p>Amendment to protocol and PIL to clarify where MRI images will be analysed. Amendment to publication policy. Amendment to protocol in relation to minor temperature deviations of study medication. Addition of sub-study to investigate blood plasma nitrite levels and methaemoglobin. Amendment to sample size. Clarification of inclusion criteria that patients with posterior infarcts with ST depression which meet the inclusion criteria can also be included.</p> <p>(REC and Regulatory Authority)</p>
31 October 2012	<p>A change in the time-point at which the primary end-point is assessed. For scientific and logistical reasons, we propose to revert to measuring the primary end-point (infarct size) at the first MRI scan (6-8 days after infarct). This has been discussed with the Trial Steering Committee and they have ratified our proposal. Infarct size at 6 months will become a secondary endpoint.</p> <p>All MRI scans will be analysed in Aberdeen. We propose that there will be no transfer of images to Imperial College London. All scans will be assessed by a blinded observer. A second blinded observer will analyse a sample of images. We also propose to amend the patient information leaflet to take account of this change.</p> <p>Proposed sample size. To take account of our proposed change to the time-point at which the primary end-point is assessed, we have revised the section on proposed sample size. To account for loss of outcome measure due to death, those who decline MRI or are unsuitable for MRI due to renal dysfunction and those in whom the MRI scans are technically inadequate, we plan to recruit approximately 200-210 participants.</p> <p>(REC only)</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Exclusion of participant's post-randomisation (either ineligible, or declined to give fully informed consent to remain in the study) Missing outcome data
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Notes: