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The effects of intravenous sodium nitrite in acute ST elevation myocardial infarction: a randomised controlled trial

Presented by Dr Nishat Siddiqi on behalf of:

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MRC Medical Research Council

Ischaemia-reperfusion-injury

- Can account for up to 50% of final infarct size
- Due to opening of mitochondrial permeability transition pore (MPTP) approx 3 minutes after reperfusion
- Various pharmacological and non pharmacological ('conditioning') strategies applied prior to or during ischaemia substantially reduce cardiac IRI in experimental models
- However there is inconsistent translation into humans

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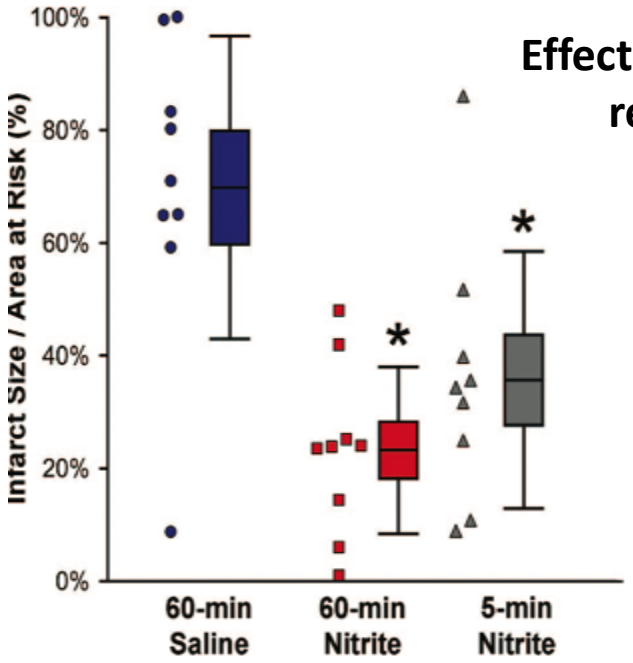
Nitrite as a cytoprotective agent

- Nitrite potently protects against IRI in heart and other organs in a variety of experimental models

Murrillo D et al Nitric Oxide 2011



Effects of sodium nitrite administered prior to reperfusion in canine acute MI model

Gonzalez et al Circulation 2008

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Hypothesis: Sodium Nitrite given intravenously immediately before opening of the infarct related artery in patients with first STEMI reduces IRI

Design

- Phase II, multicentre, randomised, double blind, placebo controlled, parallel group trial at 4 sites
- 70 micromoles sodium nitrite in 5mls saline or matching placebo administered iv over 5 mins immediately prior to opening of infarct related artery.
- Dose (per kg) and duration based on Gonzalez et al canine study

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Eligibility

- Presenting within 12 hours of onset of first STEMI
- TIMI 0 or 1 flow of the infarct related artery
- Exclusion:
  - Historical or ECG evidence of prior MI
  - Prior CABG
  - Prior PCI in the same vascular territory
  - Cardiac arrest or cardiogenic shock
  - LMS occlusion
  - Contraindication to CMR
  - Not of Northern European descent

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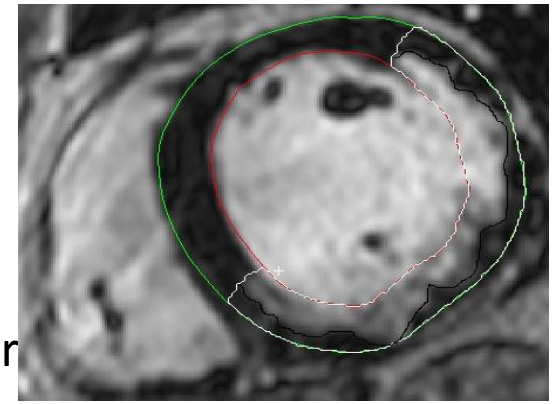
NIAMI – end points

Primary

- Infarct size (planimetry) in active vs placebo groups, measured using CMR LGE at 6-8 days (with AAR (ESA), recruitment site and diabetes status as covariates)



Secondary

- Plasma CK and Troponin I area under curve (72 hrs)
- Infarct size (LGE ,5SD) at 6-8 days corrected for AAR (T2 weighted, 2SD cutoff) as covariate
- Final infarct size (planimetry) measured by LGE at 6 months
- LVEDV, LVESV, and LVEF measured at 6-8 days and 6 months

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Sample size calculations

- 150 first MRIs provide 90% power with alpha 0.05 to detect 4% absolute difference in infarct size at 6-8 days.
- Plan - recruit approximately 210 patients assuming 160 would have a CMR at 6-8 days

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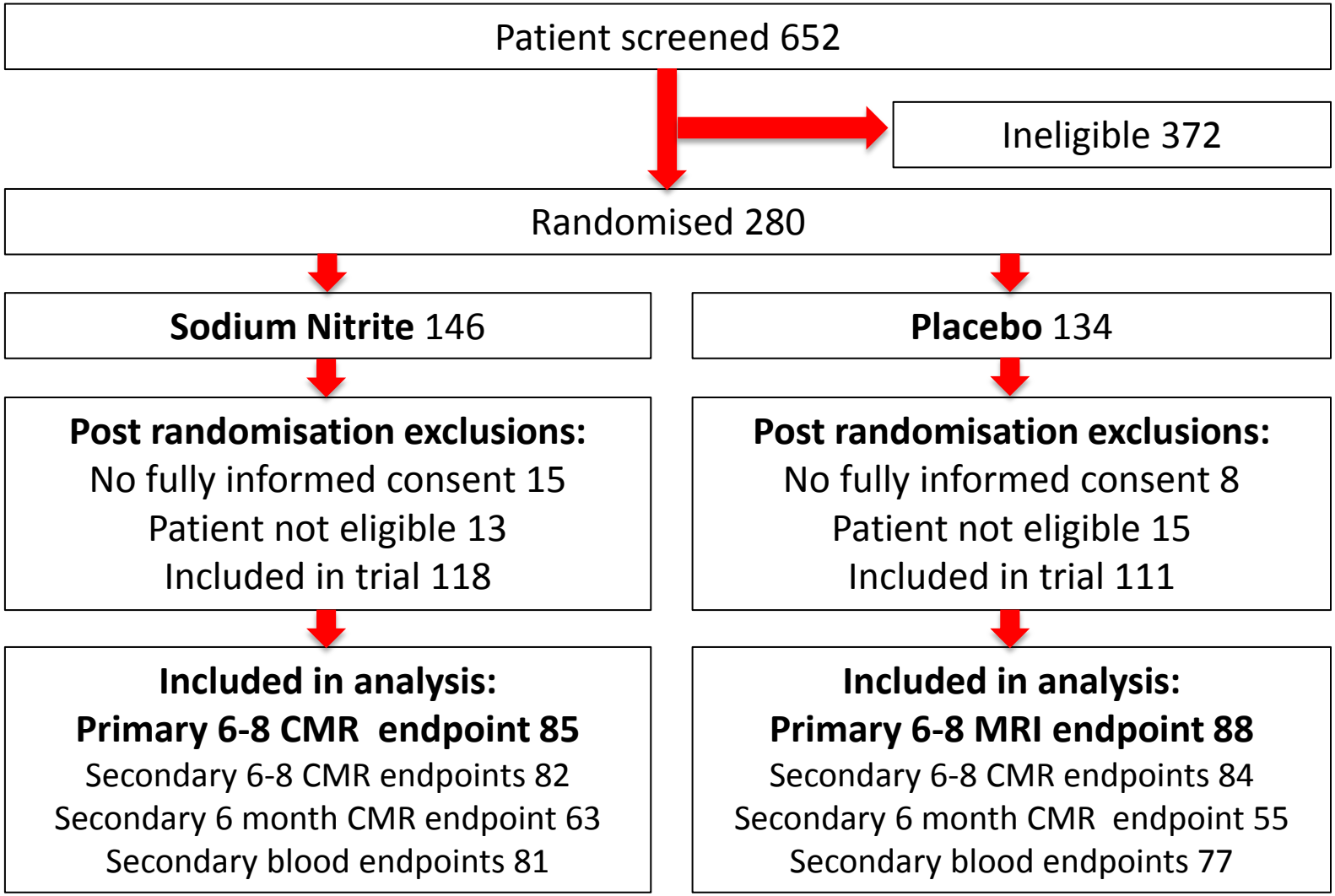
Consort diagram



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Baseline characteristics

	Nitrite (n=118)	Placebo (n=111)
Age (mean, sd)	63 (12)	64 (13)
Female n(%)	22 (19)	30 (26)
Hypertension n(%)	35(30)	35(32)
Hyperlipidaemia n(%)	55(47)	52 (46)
Diabetes n(%)	14 (12)	19 (17)
Current smoker n(%)	53(45)	47(42)
Anterior location n (%)	46 (39)	41 (37)
Pain to balloon time Median, mins (25^{th} 75^{th})	164 (127, 256)	203 (133, 317)
TIMI grade 0 pre PCI n (%)	101 (91)	105 (89)
Nitrates n (%)	99 (84)	105 (95)
Morphine n(%)	70 (59)	66 (60)

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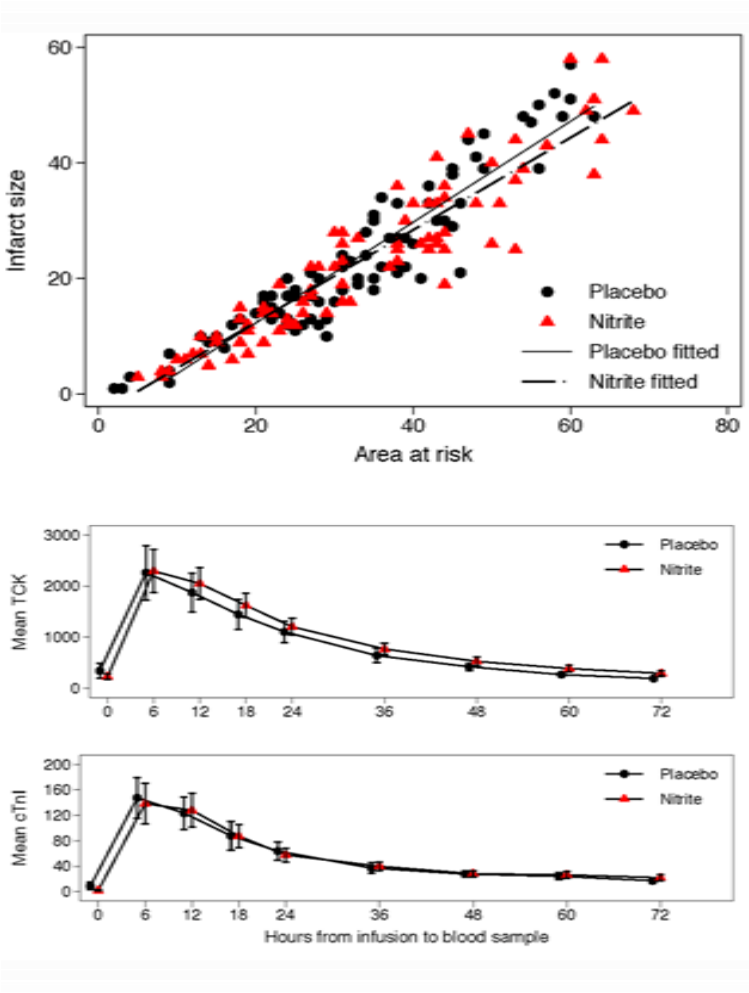
Pre-specified primary and secondary outcomes – early

Nitrite Mean (sd)	Placebo Mean (sd)	Effect size (95% CI); p value
Primary outcome: Infarct size at 6-8 days		
22.9 (13.5)	**23.1 (13.2)**	**-0.7 (-2.2, 0.7); 0.34**
Area at risk		
33.1 (15.8)	32.4 (14.1)	
Secondary outcome: Troponin I AUC		
3734 (3091)	3807 (3262)	-125 (-1139, 888); 0.81
Secondary outcome: Creatine Kinase AUC		
67019 (42446)	59574 (48337)	5766 (-8695, 20288); 0.79

NB: All other secondary outcomes (different CMR methods; 5SD, T2 AAR and LV volumes) from early scan were similar and showed no treatment effect.



Pre-specified secondary outcomes
6 month CMR

Measure	Nitrite (n=63)	Placebo (n=55)	Effect size (95% CI); p
Final infarct size mean (SD)	13.3 (8.7)	15.0 (9.7)	-0.9 (-3.4, 1.5); 0.45
LVEDV (ml) mean (SD)	159 (42)	165 (37)	-5.0 (-19.8, 9.8); 0.50
Ch LVEDV (ml) mean (SD)	-1 (29)	-3 (32)	1.3 (-10.1, 12.6); 0.82
LVESV (ml) mean (SD)	75 (31)	78 (28)	-2.7 (-13.7, 8.3); 0.63
Ch LVESV (ml) mean (SD)	9 (25)	6 (24)	2.0 (-7.2, 11.2); 0.66
LVEF (%) mean (SD)	53 (9)	53 (9)	-0.6 (-3.9, 2.7); 0.72
Ch LVEF (%) mean (SD)	-5 (8)	-3 (22)	-1.7 (-7.6, 4.2); 0.57

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Subgroup analyses

		Effect size (95% CI); p value
Pre- specified	Non- diabetics	-0.2 (-1.8, 1.3); 0.77
	Diabetics	-4.5 (-8.8, -0.2); 0.041
	Interaction	-4.3 (-8.9, 0.3); 0.067

Post-hoc sub-group analyses

No interaction between treatment effect and

- infarct site (anterior versus the remainder);
- in patients with chest pain to PCI times less than 120 minutes versus the remainder;
- in those with or without microvascular obstruction (50% in each group);
- those with an AAR of 40% or less versus more than 40%.

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Plasma nitrite levels

- Performed immediately prior to and 5 minutes after ceasing the 5 min sodium nitrite infusion in 17 patients (11 nitrite and 6 placebo)
- Plasma nitrite (micromole/l) increased from a mean (SD) of 0.76 (0.14) to 1.42 (0.96) in the treatment group but fell from 0.73 (0.08) to 0.18 (0.08) in the placebo group, p=0.008 for difference at 10 minutes.
- The fall in the placebo group was not due to haemolysis.

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CONCLUSION

A 5 minute intravenous infusion of sodium nitrite administered immediately prior to PPCI does not reduce myocardial infarct size

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