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

Presented by Dr Nishat Siddiqi on behalf of:
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
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
NIAMI

**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
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
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
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
Patient screened 652

Randomised 280

Sodium Nitrite 146

Post randomisation exclusions:
No fully informed consent 15
Patient not eligible 13
Included in trial 118

Included in analysis:
Primary 6-8 CMR endpoint 85
Secondary 6-8 CMR endpoints 82
Secondary 6 month CMR endpoint 63
Secondary blood endpoints 81

Placebo 134

Post randomisation exclusions:
No fully informed consent 8
Patient not eligible 15
Included in trial 111

Included in analysis:
Primary 6-8 MRI endpoint 88
Secondary 6-8 CMR endpoints 84
Secondary 6 month CMR endpoint 55
Secondary blood endpoints 77
<table>
<thead>
<tr>
<th></th>
<th>Nitrite (n=118)</th>
<th>Placebo (n=111)</th>
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<tbody>
<tr>
<td>Age (mean, sd)</td>
<td>63 (12)</td>
<td>64 (13)</td>
</tr>
<tr>
<td>Female n(%)</td>
<td>22 (19)</td>
<td>30 (26)</td>
</tr>
<tr>
<td>Hypertension n(%)</td>
<td>35 (30)</td>
<td>35 (32)</td>
</tr>
<tr>
<td>Hyperlipidaemia n(%)</td>
<td>55 (47)</td>
<td>52 (46)</td>
</tr>
<tr>
<td>Diabetes n(%)</td>
<td>14 (12)</td>
<td>19 (17)</td>
</tr>
<tr>
<td>Current smoker n(%)</td>
<td>53 (45)</td>
<td>47 (42)</td>
</tr>
<tr>
<td>Anterior location n (%)</td>
<td>46 (39)</td>
<td>41 (37)</td>
</tr>
<tr>
<td>Pain to balloon time Median, mins (25th 75th)</td>
<td>164 (127, 256)</td>
<td>203 (133, 317)</td>
</tr>
<tr>
<td>TIMI grade 0 pre PCI n (%)</td>
<td>101 (91)</td>
<td>105 (89)</td>
</tr>
<tr>
<td>Nitrates n (%)</td>
<td>99 (84)</td>
<td>105 (95)</td>
</tr>
<tr>
<td>Morphine n(%)</td>
<td>70 (59)</td>
<td>66 (60)</td>
</tr>
</tbody>
</table>
Pre-specified primary and secondary outcomes – early

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

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

<table>
<thead>
<tr>
<th>Pre-specified</th>
<th>Effect size (95% CI); p value</th>
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<tbody>
<tr>
<td>Non-diabetics</td>
<td>-0.2 (-1.8, 1.3); 0.77</td>
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<tr>
<td>Diabetics</td>
<td>-4.5 (-8.8, -0.2); 0.041</td>
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<tr>
<td>Interaction</td>
<td>-4.3 (-8.9, 0.3); 0.067</td>
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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%.
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.
CONCLUSION

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

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Trial Steering Committee: Professor Nicholas Boon, Professor Allan Struthers, Dr William Toff

Data Safety and Monitoring Committee: Professor Henry Dargie, Professor Chim Lang, Dr Peter Nightingale

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