BHF Glyceryl trinitrate for pre-hospital ultra-acute stroke: Main results from the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2)

Philip M Bath
Stroke Association Professor of Stroke Medicine
On behalf of RIGHT-2 Investigators
Declarations

RIGHT-2:
▲ Funded by British Heart Foundation

Philip Bath:
▲ Stroke Association Professor of Stroke Medicine
▲ NIHR Senior Investigator

Glyceryl trinitrate (GTN, nitroglycerin):
▲ Not licensed for acute stroke
Thanks

**Trial Steering Committee**
Independent experts:
- Graham Venables (TSC Chair/Neurologist; Sheffield), Pierre Amarenco (Neurologist; Paris, France), Keith Muir (Neurologist; Glasgow)

Grant holders:
- Philip Bath (Chief Investigator/Stroke Physician; Nottingham), Tim England (Stroke Physician; Derby), Nikola Sprigg (Stroke Physician; Nottingham), Alan Montgomery (Statistician; Nottingham), Stuart Pocock (Statistician; London), John Potter (Stroke Physician; Norwich), Chris Price (Stroke Physician; Newcastle), Tom Robinson (Stroke Physician; Leicester), Christine Roffe (Stroke Physician; Stoke-on-Trent), Niro Siriwardena (Pre-Hospital Healthcare; Lincoln), Joanna Wardlaw (Neuroradiologist; Edinburgh)

Funder's representative: Shannon Amoils (London)
Patient representative: Malcolm Jarvis (Nottingham)
Sponsor's representative: Angela Shone (Nottingham)

**Advisory Committee**
- Craig Anderson (Sydney, Australia), Eivind Berge (Oslo, Norway), Peter Rothwell (Oxford, UK), Steve Phillips (Halifax, Canada), Else Sandset (Oslo, Norway), Nerses Sanossian (Los Angeles, USA), Jeff Saver (Los Angeles, USA)

**Independent Data Monitoring Committee**
- Peter Sandercock (Chair; Edinburgh, UK): Kjell Asplund (Umeå, Sweden), Colin Baigent (Oxford, UK)

**Independent events (SAE) adjudicators**
- Marc Randall, Sandeep Ankolekar

**Neuroimaging adjudicators**
- Joanna Wardlaw (Chair; Edinburgh, UK), Lesley Cala (Perth, Australia), Grant Mair (Edinburgh, UK)

**Ambulance Services**
- Paramedics

**Hospitals**
- Coordinators

And the Patients and Relatives
Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial

The RIGHT-2 Investigators*

Summary
Background High blood pressure is common in acute stroke and is a predictor of poor outcome; however, large trials of lowering blood pressure have given variable results, and the management of high blood pressure in ultra-acute stroke remains unclear. We investigated whether transdermal glyceryl trinitrate (GTN; also known as nitroglycerin), a nitric oxide donor, might improve outcome when administered very early after stroke onset.

Methods We did a multicentre, paramedic-delivered, ambulance-based, prospective, randomised, sham-controlled, blinded-endpoint, phase 3 trial in adults with presumed stroke within 4 h of onset, face-arm-speech-time score of 2 or 3, and systolic blood pressure 120 mm Hg or higher. Participants were randomly assigned (1:1) to receive transdermal GTN (5 mg once daily for 4 days; the GTN group) or a similar sham dressing (the sham group) in UK-based ambulances by paramedics, with treatment continued in hospital. Paramedics were unmasked to treatment, whereas participants were masked. The primary outcome was the 7-level modified Rankin Scale (mRS; a measure of functional outcome) at 90 days, assessed by central telephone follow-up with masking to treatment. Analysis was hierarchical, first in participants with a confirmed stroke or transient ischaemic attack (cohort 1), and then in all participants who were randomly assigned (intention-to-treat, cohort 2) according to the statistical analysis plan. This trial is registered with ISRCTN, number ISRCTN26986053.
Background

1. Nitric oxide is a fundamental regulatory molecule
   a) Vasodilator, anti-leukocyte, anti-platelet, neurotransmitter, ...
2. Nitric oxide (nitrite/nitrate) level low in acute stroke
3. Glyceryl trinitrate (GTN, a NO donor) safe in acute stroke
   a) ENOS (n=4011) neutral
4. GTN improves outcome in ultra-acute/hyper-acute stroke
   a) RIGHT pilot trial, ENOS-early subgroup
   b) Time-dependent: very early best
   c) Effective in both IS and ICH
5. NO donors are neuroprotective in experimental ischaemic stroke
   a) Time-dependent

Willmot et al. Hypertension 2006; 47:1209-15
Bath et al, BASC. Stroke Res Treat 2016; ID9706720
Time is brain

Only effective interventions have time-dependency:[1]

- Alteplase [2]
- Thrombectomy [3]

Large Ambulance trials feasible, at least in US
- FAST-Mag [5]

Efficacy by time for:
- Alteplase: for mRS 0-1 [34] aOR 1.75 (1.35-2.27)
- Thrombectomy: for mRS 0-2 [35] ARR 25.9% (8.3-44.4)
- GTN: for ordinal mRS acOR 1.92 (1.28-2.94)

Modified Rankin Scale

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>18.4</td>
<td>16.2</td>
<td>18.3</td>
<td>13.3</td>
<td>10.6</td>
<td>10.2</td>
<td>13.0</td>
</tr>
<tr>
<td>Magnesium</td>
<td>18.7</td>
<td>16.3</td>
<td>18.4</td>
<td>13.3</td>
<td>10.5</td>
<td>10.1</td>
<td>12.7</td>
</tr>
</tbody>
</table>

3. Fransen et al. JAMA Neurology 2015; 21 December
5. Saver et al. NEJM 2015;372:528-36

N=6,756
N=500
N=500
N=312
N=1,700
### RIGHT-2: Design

- Multicentre, parallel-group, prospective, randomised, single-blind, blinded-endpoint controlled trial

- Main phase: May 2015 – April 2018
- 850 patients from 5+ ambulance services and 30+ associated acute hospital stroke centres
- Primary outcome/analysis at day 90: modified Rankin scale

**Diagram:**

- Day 0
  - GTN
  - No GTN
- Day 4
- Day 90

**References:**

Appleton et al. *Int J Stroke* 2017 1 August

Protocol
Patients: Inclusion/exclusions

### Inclusion

- Patients presenting to paramedics in context of 999 ambulance call for ‘stroke’
- Ages 18 years or more
- ‘Face/Arm/Speech’ Time (FAST) score ≥2
- Time ≤4 hours of onset
- Systolic BP ≥120 mmHg
- Paramedic:
  - Trained in RIGHT-2 procedures
  - Will take patient to a participating hospital
- Written or witnessed oral consent, or relative/paramedic proxy assent

### Exclusion

- Patient at a Nursing Home
- Capillary glucose <2.5 mmol/l
- Glasgow Coma Scale <8
- Witnessed seizure/fit at presentation
- Known life expectancy <6 months
- Known to have taken a PDE5 inhibitor, e.g. sildenafil, in previous day before stroke
- Known sensitivity to Transiderm Nitro patch
- Known sensitivity to Duoderm hydrocolloid dressing

*(Appleton et al. Int J Stroke 2017 1 August)*
**Intervention & comparator**

Active patch:
- Transdermal GTN 5 mg daily
- Transderm Nitro ‘5’ (Novartis)
- Unlabelled patch in labelled sachet

Sham dressing
- Hydrocolloid dressing - 4.4 cm x 3.8 cm
- Duoderm
- Unlabelled patch in labelled sachet

4 patches (GTN/Sham) packed in a ‘first-aid’ box by Nottingham University Hospitals NHS Trust Pharmacy

Appleton et al. *Int J Stroke* 2017 1 August
Key protocol changes

Original protocol
▲ Analyse all population [1] (as in RIGHT [2])
▲ Comparison of GTN vs sham

Observation
▲ Higher than expected mimic rate (26% v 12%) so risk of dilution of treatment effect

Changed protocol (blinded to treatment assignment)
1. Increase sample size 850 → 1050 (with additional funding)
2. Change to hierarchical analysis to prevent dilution [3]
   a) Explanatory analysis in target population (stroke + TIA). If positive
   b) Pragmatic analysis in whole population (ITT)

1. Appleton *et al*. *Int J Stroke* 2017 1 August
CONSORT: in All (ITT)

Randomised 1149
  GTN 568
  Sham 581

Adherence
  First patch >99%
  First 2 patches 57%

Follow-up day 90
  mRS 1102 (96%)
  Vital status 1122 (98%)
  Died 203
  Missing 0
  Lost to follow-up 21
  Withdraw 25
  Refused 1

RIGHT-2 Investigators. *Lancet* 2019; *in press*
## Baseline, ambulance: in All (ITT)

**Balanced**

<table>
<thead>
<tr>
<th></th>
<th>GTN</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, pre-randomisation</td>
<td>568</td>
<td>581</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>72 (15)</td>
<td>73 (15)</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>294 (52)</td>
<td>300 (52)</td>
</tr>
<tr>
<td><strong>OTR (mins)</strong></td>
<td>70 [45-115]</td>
<td>72 [45-118]</td>
</tr>
<tr>
<td>ECG, AF/flutter (%)</td>
<td>92 (21)</td>
<td>95 (20)</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>162 (25)</td>
<td>163 (26)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>92 (19)</td>
<td>92 (17)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>82 (18)</td>
<td>83 (19)</td>
</tr>
<tr>
<td>GCS &lt;14 (%)</td>
<td>162 (29)</td>
<td>140 (24)</td>
</tr>
<tr>
<td><strong>FAST =3 (%)</strong></td>
<td>343 (60)</td>
<td>347 (60)</td>
</tr>
<tr>
<td>Ethnic, non-white (%)</td>
<td>50 (9)</td>
<td>63 (11)</td>
</tr>
<tr>
<td>Pre-morbid mRS &gt;2 (%)</td>
<td>115 (20)</td>
<td>108 (19)</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>137 (25)</td>
<td>135 (24)</td>
</tr>
<tr>
<td><strong>Ischaemic stroke (%)</strong></td>
<td>302 (53)</td>
<td>295 (51)</td>
</tr>
<tr>
<td>Intracerebral haemorrhage (%)</td>
<td>74 (13)</td>
<td>71 (12)</td>
</tr>
<tr>
<td>TIA (%)</td>
<td>57 (10)</td>
<td>52 (9)</td>
</tr>
<tr>
<td>Mimic (%)</td>
<td>134 (24)</td>
<td>163 (28)</td>
</tr>
</tbody>
</table>

**Of stroke (n=743)**

- IS 80%
- ICH 20%

RIGHT-2 Investigators. *Lancet* 2019; *in press*
SBP/DBP (mmHg): in Stroke/TIA

RIGHT-2 Investigators. Lancet 2019; in press
Primary outcome: in Stroke/TIA

Poor outcome acOR 1.25 (0.97, 1.60), p=0.083

> Trial neutral in target population

RIGHT-2 Investigators. *Lancet* 2019; *in press* N=828
mRS by subgroups: in Stroke/TIA

One interaction:
▲ Time: GTN worse when given very early

No interactions:
▲ Age
▲ Sex
▲ Pre-morbid mRS
▲ HT
▲ Previous stroke
▲ Previous nitrate
▲ GCS
▲ FAST
▲ SBP
▲ AF
▲ Diagnosis

RIGHT-2 Investigators. *Lancet* 2019; *in press*
Death: in Stroke/TIA

GTN  Sham
23%  19%  aHR 1.24 (0.91, 1.68), p=0.17

> No difference in death

RIGHT-2 Investigators. Lancet 2019; in press
Primary outcome (mRS): in All (ITT)

Explanatory analysis not positive so hierarchical pragmatic analysis not necessary, but N=1102

GTN

Sham

Poor outcome acOR 1.04 (0.84, 1.29), p=0.69

> Neutral trial in intention-to-treat population

RIGHT-2 Investigators. Lancet 2019; in press
**Strengths**

- Large pre-hospital trial
- Very early treatment [71 mins]
- Blinded outcomes
- Blinded adjudication
- Good compliance to first treatment
- Hierarchical analysis novel – potentially useful for future trials

**Limitations**

- Single-blind trial
- UK-only trial
- Change to protocol
- Smaller than expected BP difference
- Lower than expected adherence on days 2-4
- Higher than expected mimic rate
Summary

UK multicentre ambulance-based paramedic-led trial:
 ▲ Feasible (supports FAST-MAG)

GTN:
In stroke/TIA (target)
 ▲ mRS: Neutral

In All (ITT)
 ▲ mRS: Neutral
    ▲ Mimics: Safe
    ▲ SAEs: Neutral

RIGHT-2 vs ENOS-early
 ▲ Neutral vs positive
 ▲ OTR: 71 mins vs 264 mins

GTN
 ▲ No indication for use by paramedics pre-hospital

RIGHT-2 Investigators. Lancet 2019; in press
Thank you for listening

And many thanks to patients, investigators and our families