# 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


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- Paramedics

**Hospitals**

- Coordinators

And the Patients and Relatives

# Publication: Lancet 6 Feb 2019

## 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.


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See Online for appendix

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# 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


Rashid *et al*. *J Stroke Cerebrovasc Dis* 2003; 12: 82-87
Willmot *et al*. *Hypertension* 2006; 47:1209-15
ENOS Trial Investigators. *Lancet* 2015; 385: 617-28
Bath *et al,* BASC. *Stroke Res Treat* 2016; ID9706720
Willmot *et al*. *Nitric Oxide* 2005; 12: 141-9

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# Time is brain

Only effective interventions have time-dependency:[1]

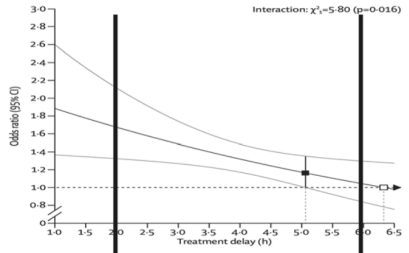
- ▲ Alteplase [2]
- ▲ Thrombectomy [3]
- ▲ GTN? Pilot data [4]

Large Ambulance trials feasible, at least in US

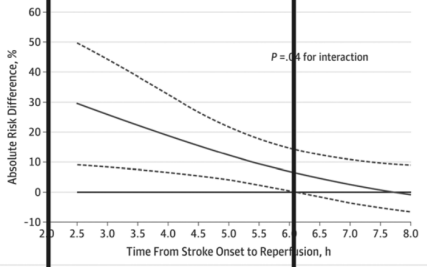
- ▲ FAST-Mag [5]

Efficacy by time for:

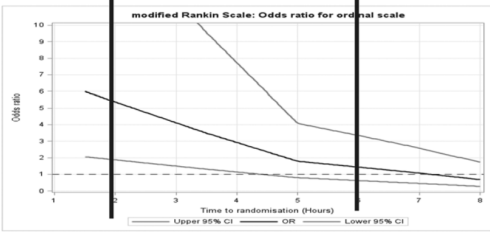
Alteplase: for mRS 0-1 [34]
aOR 1.75 (1.35-2.27)

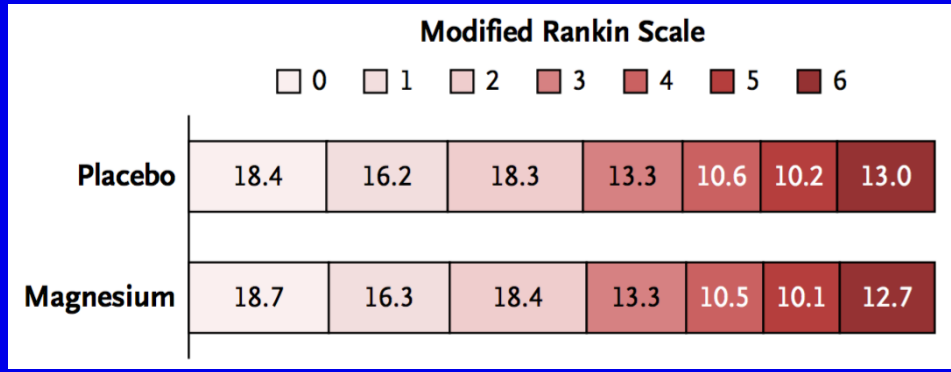



Thrombectomy: for mRS 0-2 [35]
ARR 25.9% (8.3-44.4)




GTN: for ordinal mRS
acOR 1.92 (1.28-2.94)



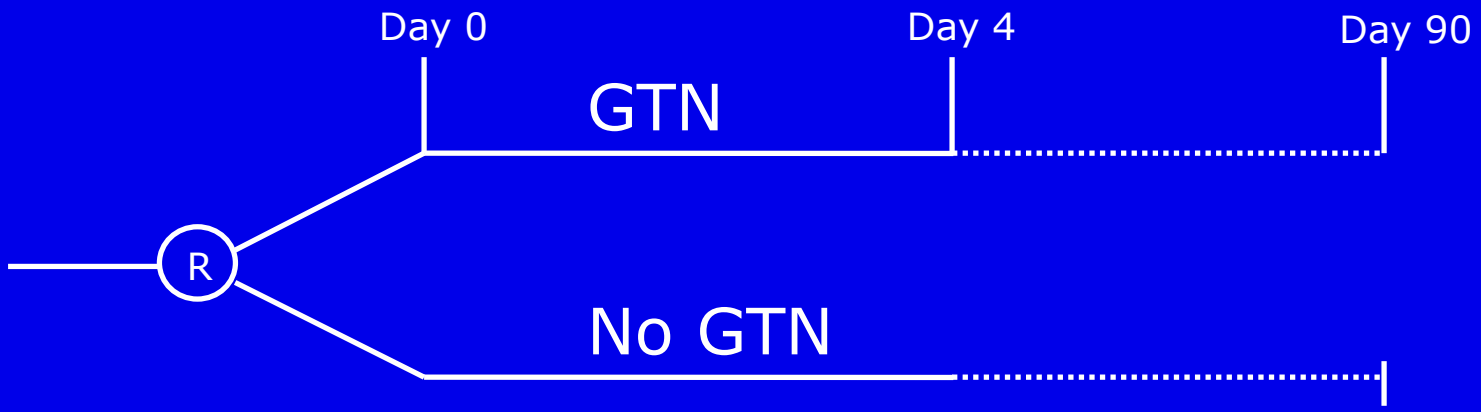





1. Bath. *Stroke* 2016; 47:2423-6
2. Emberson *et al*. *Lancet 2014*; 384: 1929-35 N=6,756
3. Fransen *et al*. *JAMA Neurology* 2015; 21 December N= 500
4. Bath, Woodhouse *et al*. *Stroke Res Treat* 2016; 9706720 N= 312
5. Saver *et al*. *NEJM* 2015;372:528-36 N=1,700

# 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

# 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

# Intervention & comparator

Active patch:

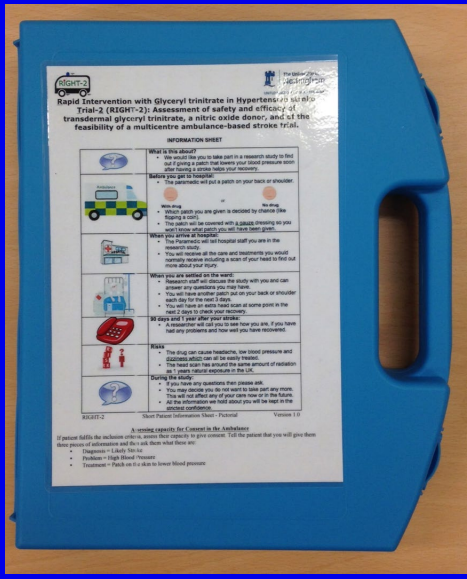
- Transdermal GTN 5 mg daily
- Transiderm Nitro '5' (Novartis)
- Unlabelled patch in labelled sachet

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
2. Ankolekar *et al*. *Stroke* 2013; 44: 3120-8
3. Scutt *et al*. *Eur J Stroke* 2018; 3 Jan


Protocol
N=41
SAP

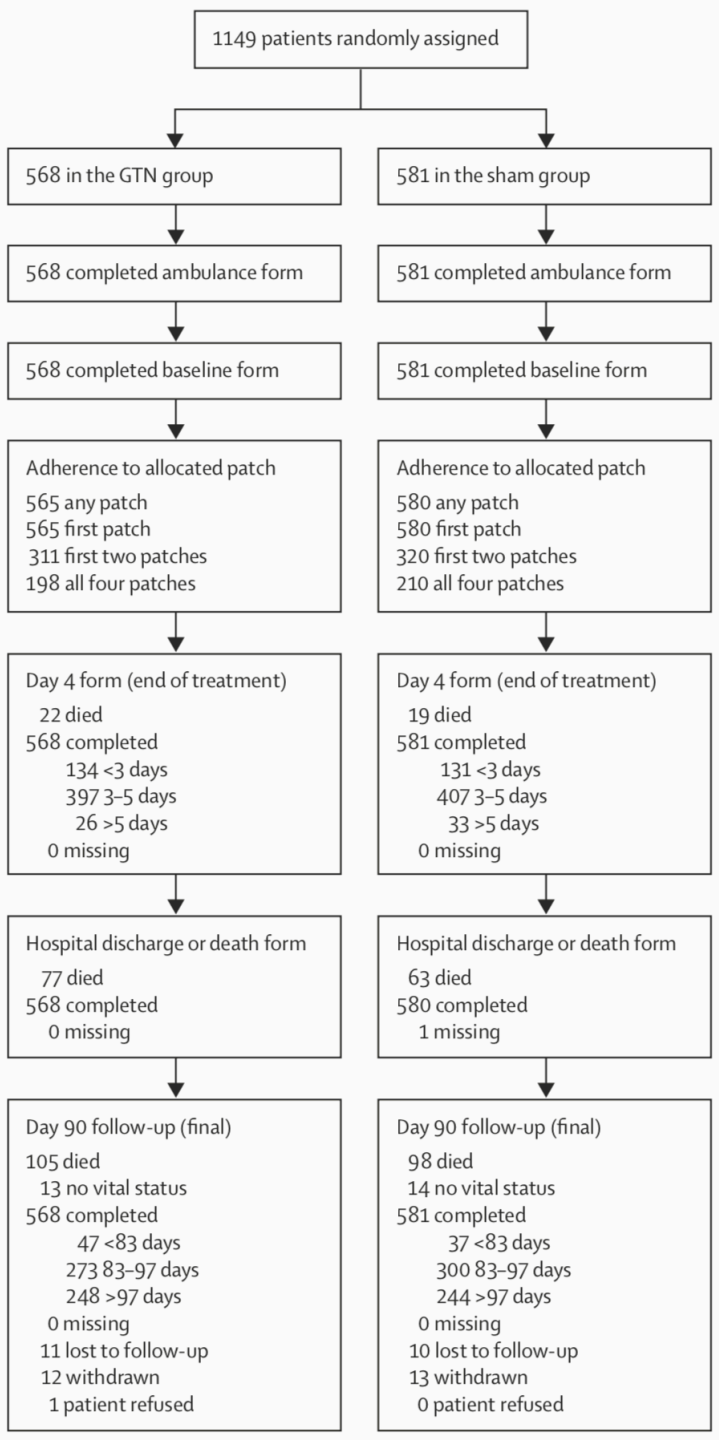
# CONSORT: in All (ITT)

| | |
|---|---|
| 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

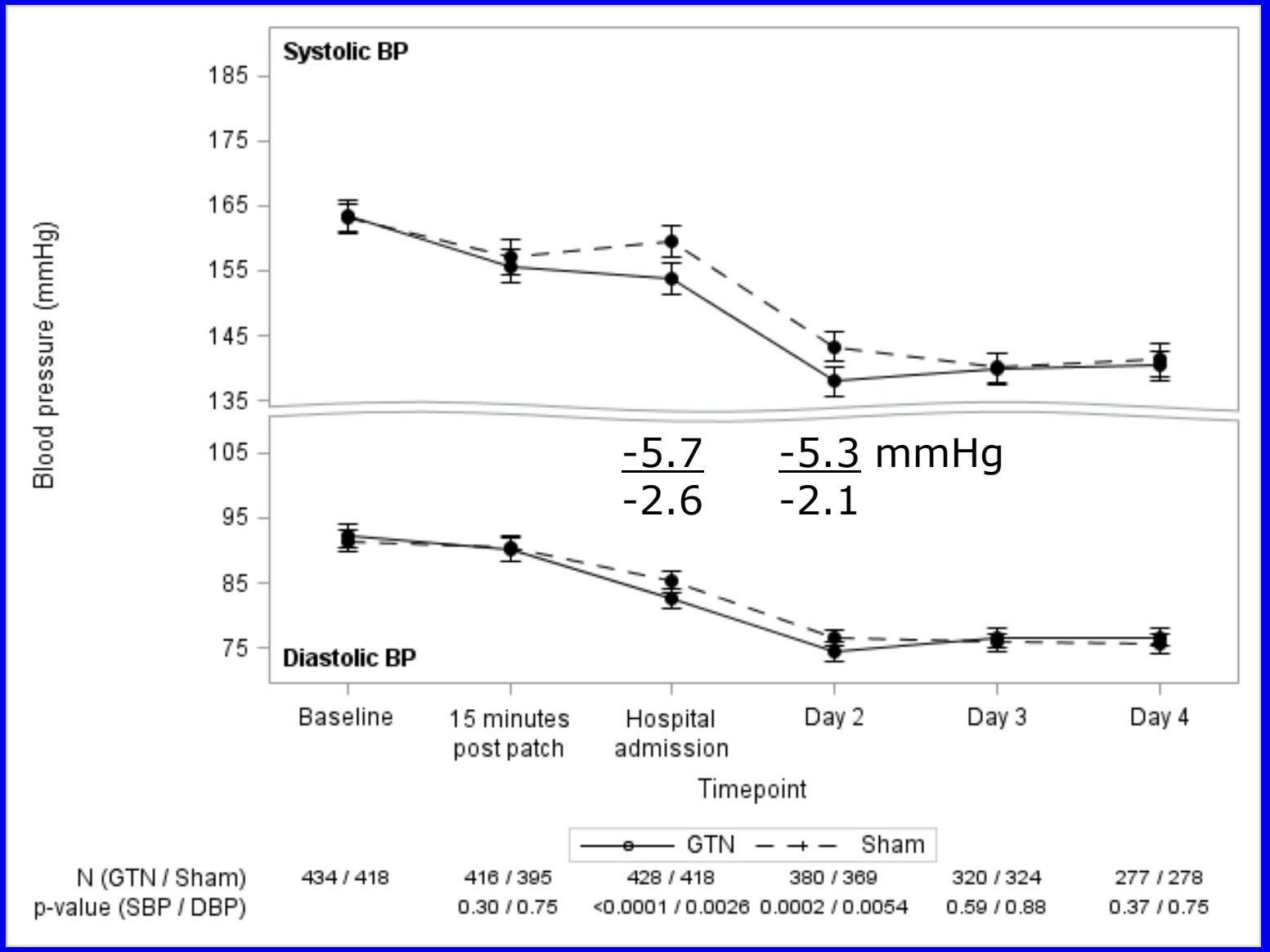
| | GTN | Sham |
|---|---|---|
| N, pre-randomisation | 568 | 581 |
| **Age (years)** | **72 (15)** | **73 (15)** |
| Sex, male (%) | 294 (52) | 300 (52) |
| **OTR (mins)** | **70 [45-115]** | **72 [45-118]** |
| ECG, AF/flutter (%) | 92 (21) | 95 (20) |
| **SBP (mmHg)** | **162 (25)** | **163 (26)**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

Of stroke (n=743)

- IS 80%
- ICH 20%

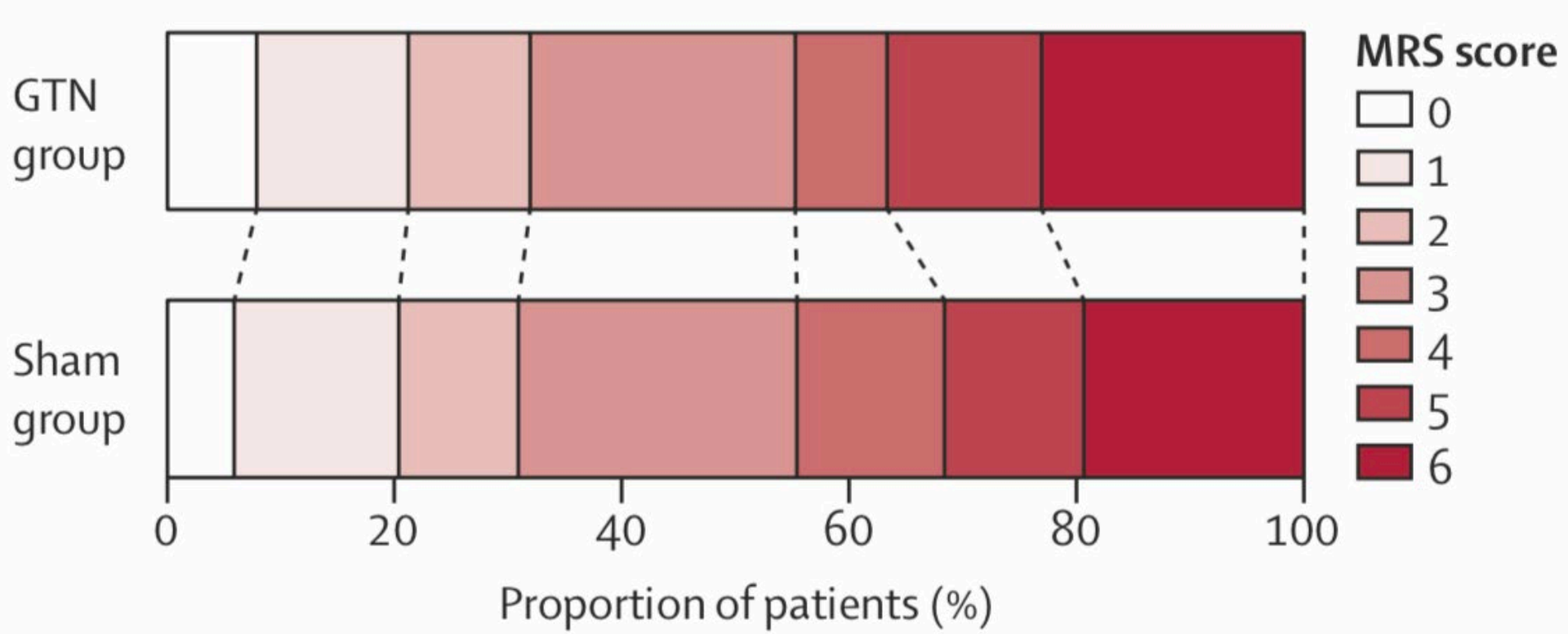
RIGHT-2 Investigators. *Lancet* 2019; *in press*

# 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*

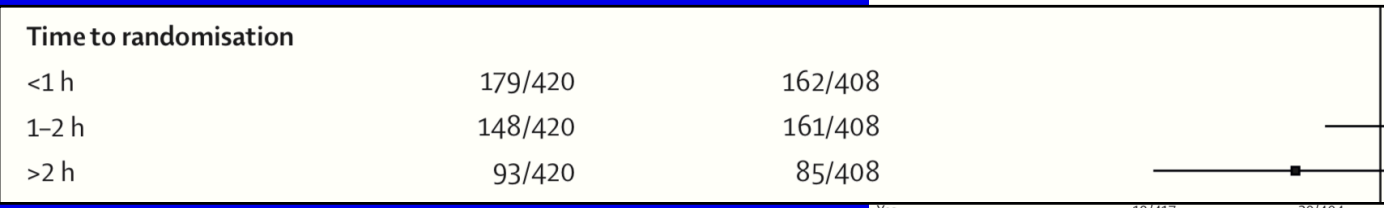
RIGHT-2 Investigators. *Lancet* 2019; *in press*

N=828

# mRS by subgroups: in Stroke/TIA

One interaction:

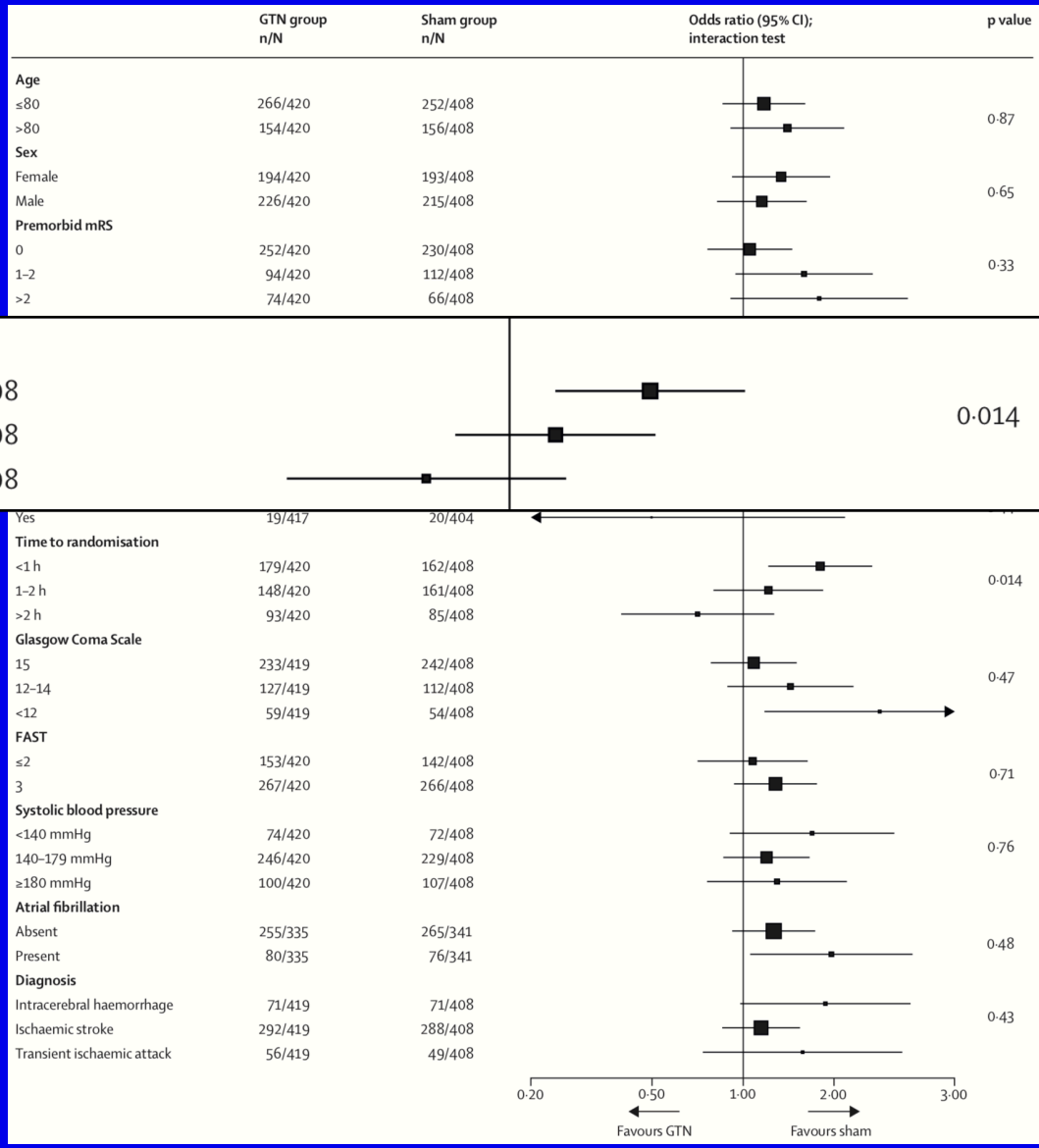
- Time: GTN worse when given very early



| | GTN group n/N | Sham group n/N | p value |
|---|---|---|---|
| **Time to randomisation** | | | |
| <1 h | 179/420 | 162/408 | 0·014 |
| 1–2 h | 148/420 | 161/408 | |
| >2 h | 93/420 | 85/408 | |

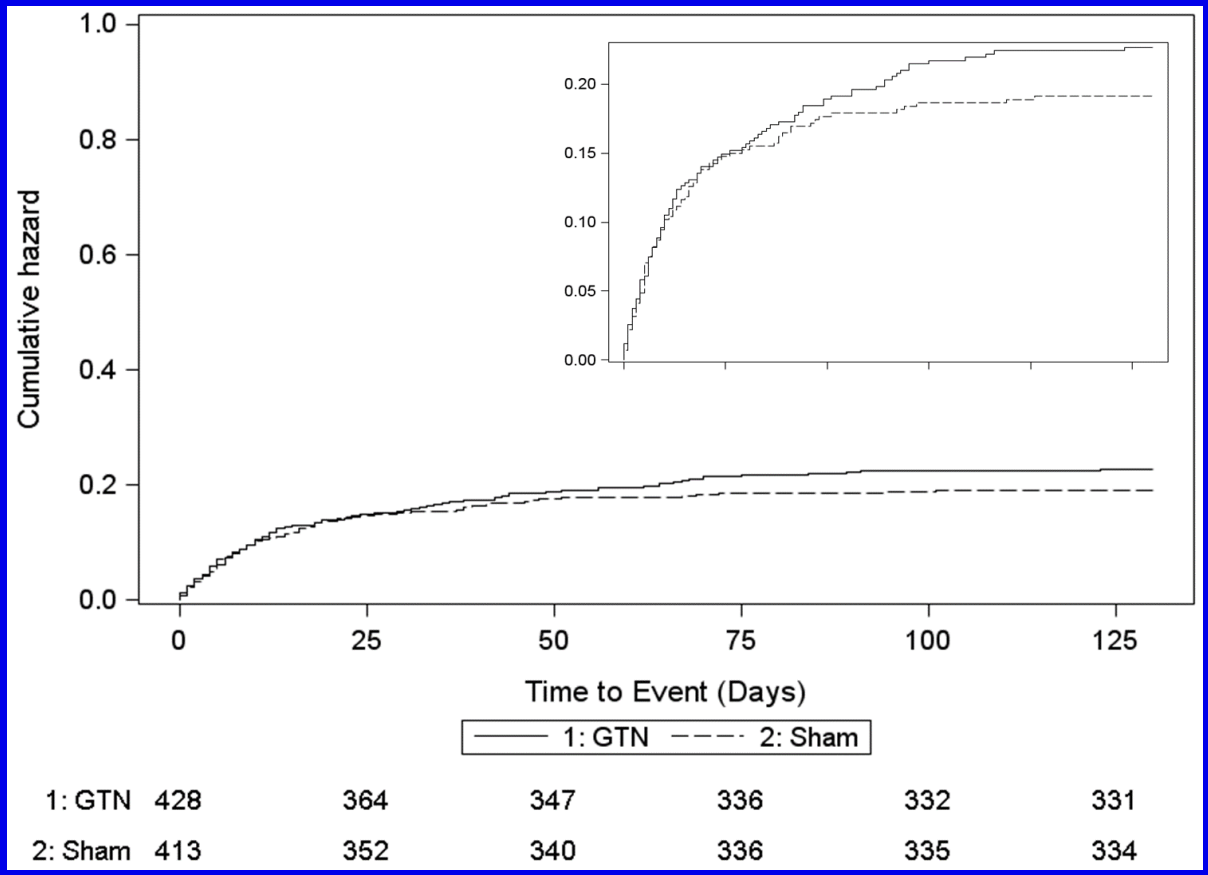
No interactions:

- 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*

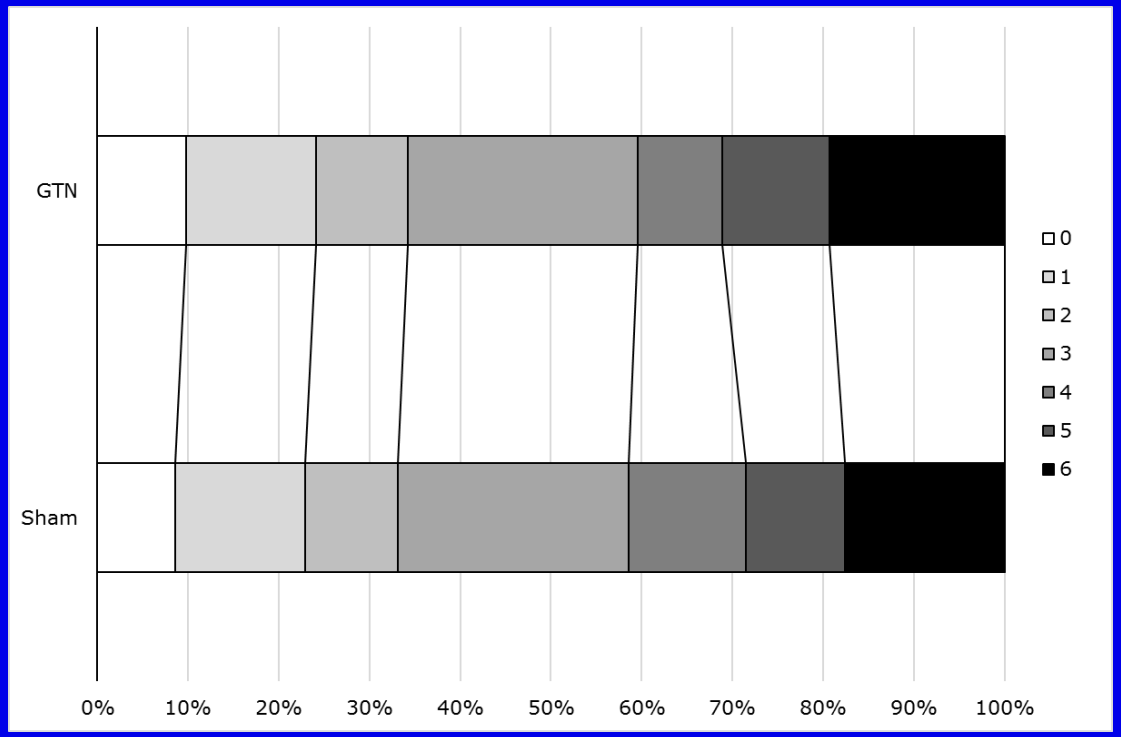
# Primary outcome (mRS): in All (ITT)

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*

N=1102

# 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*

RIGHT-2

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# Thank you for listening

And many thanks to patients, investigators and our families

Stroke association

British Heart Foundation