SVN Stroke & Vascular Neurology

Prehospital transdermal glyceryl trinitrate for ultra-acute ischaemic stroke: data from the RIGHT-2 randomised sham-controlled ambulance trial

Jason Philip Appleton ,[1,2] Lisa J Woodhouse ,[3] Craig S Anderson,[4,5,6] Sandeep Ankolekar,[7] Lesley Cala,[8] Mark Dixon,[3,9] Timothy J England,[3] Kailash Krishnan ,[10] Grant Mair,[11] Keith W Muir,[12] John Potter,[13] Christopher I Price,[14] Marc Randall,[15] Thompson G Robinson,[16] Christine Roffe,[17] Else C Sandset,[18,19] Jeffrey L Saver,[20] Angela Shone,[21] Aloysius Niroshan Siriwardena,[9,22] Joanna M Wardlaw ,[11] Nikola Sprigg,[3,10] Philip M Bath ,[3,10] On behalf of the RIGHT-2 Investigators

To cite: Appleton JP, Woodhouse LJ, Anderson CS, *et al*. Prehospital transdermal glyceryl trinitrate for ultra-acute ischaemic stroke: data from the RIGHT-2 randomised sham-controlled ambulance trial. *Stroke & Vascular Neurology* 2024;**9**: e001634. doi:10.1136/svn-2022-001634

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/svn-2022-001634).

JPA and LJW contributed equally.

Received 14 April 2022
Accepted 12 August 2022
Published Online First 8 June 2023

For numbered affiliations see end of article.

Correspondence to
Professor Philip M Bath; philip.bath@nottingham.ac.uk

ABSTRACT

Background The effect of transdermal glyceryl trinitrate (GTN, a nitrovasodilator) on clinical outcome when administered before hospital admission in suspected stroke patients is unclear. Here, we assess the safety and efficacy of GTN in the prespecified subgroup of patients who had an ischaemic stroke within the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2).

Methods RIGHT-2 was an ambulance-based multicentre sham-controlled blinded-endpoint study with patients randomised within 4 hours of onset. The primary outcome was a shift in scores on the modified Rankin scale (mRS) at day 90. Secondary outcomes included death; a global analysis (Wei-Lachin test) containing Barthel Index, EuroQol-5D, mRS, telephone interview for cognitive status-modified and Zung depression scale; and neuroimaging-determined 'brain frailty' markers. Data were reported as n (%), mean (SD), median [IQR], adjusted common OR (acOR), mean difference or Mann-Whitney difference (MWD) with 95% CI.

Results 597 of 1149 (52%) patients had a final diagnosis of ischaemic stroke; age 75 (12) years, premorbid mRS>2 107 (18%), Glasgow Coma Scale 14 (2) and time from onset to randomisation 67 [45, 108] min. Neuroimaging 'brain frailty' was common: median score 2 [2, 3] (range 0–3). At day 90, GTN did not influence the primary outcome (acOR for increased disability 1.15, 95% CI 0.85 to 1.54), death or global analysis (MWD 0.00, 95% CI −0.10 to 0.09). In subgroup analyses, there were non-significant interactions suggesting GTN may be associated with more death and dependency in participants randomised within 1 hour of symptom onset and in those with more severe stroke.

Conclusions In patients who had an ischaemic stroke, ultra-acute administration of transdermal GTN in the ambulance did not improve clinical outcomes in a population with more clinical and radiological frailty than seen in previous in-hospital trials.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Transdermal glyceryl trinitrate (GTN) was associated with less death and dependency in those with acute stroke treated within 6 hours of stroke onset in a systematic review and individual patient data meta-analysis from two randomised controlled trials. The Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) assessed the effect of GTN given prehospital in patients with presumed stroke within 4 hours of onset. This subgroup analysis details the effect of GTN in those with clinically diagnosed ischaemic stroke.

WHAT THIS STUDY ADDS

⇒ Transdermal GTN did not influence clinical or radiological outcomes despite lowering blood pressure compared with sham. GTN may be associated with more death and dependency in those randomised within 1 hour of symptom onset and in those with more severe stroke, but these interactions were non-significant. The population recruited in RIGHT-2 was more dependent and frailer (both clinically and radiologically) than in prior trials of transdermal GTN within 6 hours of stroke onset performed in hospital, and may account for the differences in results.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Transdermal GTN should not be administered to patients with presumed stroke prehospital outside of a trial environment. Clinical and radiological frailty should be taken into consideration in the design and interpretation of future ultra-acute stroke trials.

INTRODUCTION

In patients presenting with acute ischaemic stroke, high blood pressure (BP) is common and associated with a worse clinical outcome, by leading to early cerebral oedema and recurrent ischaemia.[1 2] However, moderate-to-large trials in acute ischaemic stroke assessing BP-lowering medications have given conflicting results: the China Antihypertensive

Trial in Acute Ischaemic Stroke (CATIS)[3] and ischaemic stroke subgroups of the Scandinavian Candesartan Acute Stroke trial (SCAST)[4 5] and Efficacy of Nitric Oxide in Stroke (ENOS) trial[6] were all neutral. In contrast, the β-blocker stroke trial (BEST)[7] and intravenous nimodipine west European stroke trial (INWEST)[8] involving ß-receptor antagonists and a calcium channel blocker, respectively, were harmful. However, few participants in all these trials were randomised under 12 hours from stroke onset. Intensive BP lowering in patients undergoing intravenous thrombolysis in the BP arm of the enhanced control of hypertension and thrombolysis stroke study (ENCHANTED-BP) was also neutral.[9] Consequently, how to manage elevated BP in patients with acute ischaemic stroke is unclear.[10]

Nitric oxide (NO) donors, including glyceryl trinitrate (GTN), have multiple properties that may be advantageous in acute stroke beyond BP lowering including improving cerebral perfusion, neuroprotection and anti-inflammation. Vascular NO concentrations in acute stroke are low and associated with worse clinical outcomes,[11] and therefore, supplementing low NO levels may be beneficial. In preclinical studies of permanent cerebral ischaemia models, NO donors reduced infarct size and increased cerebral blood flow, but only when given early after stroke onset.[12]

Transdermal GTN lowered BP by 6.8/4.9 mm Hg compared with no GTN in the ENOS ischaemic stroke subgroup.[6] In a systematic review and individual patient data meta-analysis using data from two randomised trials, transdermal GTN was associated with less death and dependency in 312 patients who were treated within 6 hours of stroke onset.[13] As a result, the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) was performed in 1149 patients with presumed, paramedic-assessed acute stroke within 4 hours of the onset of stroke symptoms.[14] In patients with subsequently diagnosed intracerebral haemorrhage, GTN was associated with a worse global outcome and in-hospital death, and haematoma size and mass effect were larger.[15] Here, we assess the safety and efficacy of GTN in a prespecified subgroup analysis of RIGHT-2 participants with subsequently clinically diagnosed ischaemic stroke.

METHODS

Study design and study population

RIGHT-2 was a UK, prospective, multicentre, ambulance-based, paramedic-initiated, outcome-blinded, randomised sham-controlled trial within 4 hours of symptom onset in adults with presumed stroke.[14 16–18] In brief, adult patients with presumed stroke met inclusion criteria if they presented to a trial-trained paramedic within 4 hours of symptom onset and could be conveyed to a hospital in the trial. Patients had to have systolic BP (SBP) ≥120 mm Hg and a Face-Arm-Speech-Time (FAST) score of ≥2. Patients with a reduced consciousness level (Glasgow Coma Scale (GCS) <8/15), hypoglycaemia (capillary glucose <2.5 mmol/L), witnessed seizure activity or from a nursing home were excluded. The main trial (online supplemental material) provides more detailed inclusion and exclusion criteria.[14] The trial is registered (ISRCTN26986053) and was adopted by the National Institute for Health Research Clinical Research Network and recruited patients between 22 October 2015 and 23 May 2018.

Treatment

Patients were assigned at random to receive in a 1:1 ratio either transdermal GTN (5 mg as Transiderm-Nitro 5, Novartis, Frimley UK) or sham (DuoDERM hydrocolloid dressing, Convatec, Flintshire, UK). The randomised treatment was applied by the paramedic prehospital with three further daily treatments given in hospital.

Clinical outcome measures

The primary outcome was function (death and dependency) assessed using the modified Rankin Scale (mRS, scores of 0=normal to 6=died) measured at day 90. This information was obtained using a structured questionnaire by telephone by central trained assessors blinded to treatment allocation.[19] If the participant was unable to complete the assessment, then a relative or carer was asked to provide this information. A postal version was sent out to participants if they could not be contacted by telephone.

At day 4 (or at hospital discharge, if earlier), data on adherence to treatment, neurological deterioration and non-trial management (eg, thrombolysis and thrombectomy) were recorded. Date of hospital discharge, length of stay and discharge destination were collected. Day 90 prespecified secondary clinical outcomes included: Barthel index (BI), a measure of activities of daily living; Telephone Interview for Cognition Scale-modified (TICS-M), modified telephone Mini-Mental State Examination and verbal fluency using animal naming as markers of cognition; European Quality of Life-5 dimensions-3 level (EQ-5D-3L) derived health status utility value (HSUV) and EQ-Visual Analogue Scale to assess health-related quality of life; and the abbreviated Zung Depression Score (ZDS) for mood. All as recorded in ENOS and described in the trial protocol.[6 16] Home-time was calculated as the number of days the participant spent at home from discharge to day 90.

Safety outcomes included all-cause and cause-specific mortality; investigator-reported hypotension or hypertension occurring during the 4-day treatment period; and serious adverse events (SAEs, all up to day 5 and fatal to day 90). SAEs were validated and categorised blinded to treatment allocation by expert adjudicators.

Neuroimaging

Non-enhanced brain scans (CT or MRI) performed at hospital, CT/MR angiography when performed according to local policy, and a further CT or MR scan performed on the next day to assess safety, were each collected and

centrally adjudicated by expert neuroradiologists blinded to symptoms and treatment allocation, using assessments updated from ENOS and the third international stroke trial.[6 20]

Prestroke imaging markers including cerebral atrophy, periventricular white matter lucencies and old vascular lesion(s) were assessed individually, and amalgamated into predefined scores of small vessel disease (SVD) and 'brain frailty'[20 21]:

- Cerebral atrophy: assessed separately in cortical and central regions as 0=absent, 1=moderate, 2=severe.
- Periventricular white matter lucencies: assessed in anterior and posterior regions as 0=absent, 1=lucency restricted to region adjoining ventricles, 2=lucency covering lateral ventricle to cortex.
- Old vascular lesions: assessed by location.
- SVD score: 1 point for severe periventricular white matter lucencies and 1 point for any old lacunar infarcts or lacunes (maximum 2 of 2).
- 'Brain frailty' score: 1 point for periventricular white matter lucencies (score of 1 or 2 anterior and/or posterior); 1 point for cerebral atrophy (scores of 1 or 2 cortical and/or central); and 1 point for old vascular lesion(s) (maximum 3 of 3).

Acute stroke lesions were assessed by location, size, severity, swelling and mass effect. Hyperdense artery sign was recorded and the number of arteries involved totalled (arteries sum score). The Alberta Stroke Programme Early CT Score (ASPECTS) was adapted to include the 10 regions of the middle cerebral artery as well as additional points for anterior and posterior cerebral arterial territories (0=hypoattenuation of all 12 regions, 12=no hypoattenuation in any of the 12 regions). The degree of any ischaemic change in brain tissue was graded as none (0), low (1, eg, loss of grey-white margins on CT) or high (2, eg, CT hypoattenuating relative to normal white matter).

CT/MR angiography measures included modified thrombolysis in cerebral infarction (mTICI, adapted for use on CT and MR angiography), Mori reperfusion, clot burden and arteries sum scores and collateral status. These measures were coded as ordered categorical data as follows:

- mTICI: missing=0, no flow (0)=1, minimal flow (1)=2, partial flow<50% of expected territory (2a)=3, partial flow>50% of expected territory (2b)=4, complete flow (3)=5.
- Mori: missing=0, no flow (0)=1, minimal flow (1)=2, <50% lumen patency and partial filling (<1/2) of major branches of affected artery (2a)=3, <50% lumen patency and incomplete filling (1/2) of major branches of affected artery (2b)=4, >50% lumen patency (3)=5, complete flow (4)=6.
- Collateral status: missing=0, poor=1, moderate=2, good=3.

Statistical analysis

The analyses for this prespecified subgroup followed the statistical analysis plan for the overall trial.[17] RIGHT-2 was initially powered to detect a shift in mRS with a common OR of 0.70, 5% significance, 90% power, 20% non-stroke rate, reduction for baseline covariate adjustment of 20% and 3% lost to follow-up with a sample size of 850. However, during recruitment the non-stroke diagnosis rate was in excess of 30% and therefore the sample size was increased to 1050 to account for this. The primary outcome of shift on the seven levels of the mRS was analysed by ordinal logistic regression and adjusted for age, sex, premorbid mRS, baseline SBP, baseline FAST score and time from onset to randomisation.[17] We used the likelihood ratio test to ensure the assumption of proportional odds was not violated. Unadjusted, mean, per-protocol and imputed (multiple regression-based imputation estimated any missing mRS data) sensitivity analyses were also performed. An interaction term was added to an adjusted ordinal logistic regression model to assess the heterogeneity of the effect of GTN vs sham on the primary outcome in prespecified subgroups. Other outcomes were assessed using adjusted binary or ordinal logistic regression, multiple linear regression, Cox regression and analysis of covariance (BP). A prespecified global outcome (including BI, EQ-5D-HSUV, mRS, TICS-M and ZDS) was analysed using the Wei-Lachin test.[15 22 23] All analyses were by intention to treat, unless otherwise specified. Anonymised data will be shared with the Virtual International Stroke Trials Archive and Blood pressure in Acute Stroke Collaboration.

RESULTS

Demographics

Between October 2015 and May 2018, RIGHT-2 recruited 1149 patients of whom 597 (52%, GTN 302, sham 295) had a final diagnosis of ischaemic stroke (figure 1). Ambulance and hospital admission baseline characteristics were well balanced between randomised treatment groups (table 1): mean age 75 (12) years, female 287 (48%), premorbid mRS>2 107 (18%) and FAST score=3 391 (65%). Patients were randomised at a median of 67 [45, 108] min after symptom onset with a mean BP of 161 (23)/90 (17) mm Hg. A total of 127 (26%) had atrial fibrillation or flutter in the ambulance. Following hospital admission, 284 (48%) participants received alteplase and 24 (4%) underwent mechanical thrombectomy (table 1).

Adherence to the first treatment was excellent (596, >99%) although only 451 (76%) and 307 (51%) participants received at least 2 days and all 4 days of treatment, respectively (online supplemental table 1). BP fell over the 4 days of treatment in both randomised groups. GTN lowered BP by 5.7/1.9 mm Hg as compared with sham at hospital admission and by 7.1/2.4 at day 2, but thereafter BP did not differ between GTN and sham groups (online supplemental figure 1).

Clinical outcomes

The primary outcome of mRS at day 90 was available for 580 (97%) participants (table 2); GTN did not influence

Figure 1 CONSORT diagram in participants with a final diagnosis of ischaemic stroke. CONSORT, consolidated standards of reporting trials;GTN, glyceryl trinitrate.

death and dependency (GTN 3 [2, 5] vs sham 3 [2, 5], adjusted common OR for increased dependency 1.15, 95% CI 0.85 to 1.54, p=0.36, figure 2). The proportional odds assumption was not violated (p=0.93). No significant results were seen in the four different sensitivity analyses. Although there were no statistically significant interactions of the effect of GTN on mRS in prespecified subgroups, in the time to randomisation subgroup ($p_{interaction}$=0.15) those randomised within 1 hour from onset to GTN had a shift in mRS to an unfavourable outcome (figure 3). Further, in exploratory post hoc subgroup analyses, National Institutes of Health Stroke Scale (NIHSS) >12 in those randomised to GTN was associated with an unfavourable shift in mRS, although the interaction was non-significant ($p_{interaction}$=0.055, online supplemental figure 2).

At presentation to hospital, GCS, NIHSS and FAST scores did not differ between GTN and sham groups (table 2, online supplemental figure 3). In hospital, numerically more participants randomised to GTN received intravenous thrombolysis than those randomised to sham, although this was not significant: 150 (50%)

Table 1 Baseline characteristics in participants with acute ischaemic stroke

	All	GTN	Sham
Participants	597	302	295
Ambulance data			
Age (years)	75 (12)	74 (13)	76 (12)
Sex, female (%)	287 (48)	146 (48)	141 (48)
Time (min)			
OTR	67 [45,108]	66 [44,105]	67 [45,110]
<1 hour (%)	257 (43)	138 (46)	119 (40)
1–2 hours (%)	214 (36)	101 (33)	113 (38)
>2 hours (%)	126 (21)	63 (21)	63 (21)
ECG, AF/flutter (%)	127 (26)	60 (25)	67 (27)
Systolic BP (mm Hg)	161 (23)	161 (24)	160 (23)
Diastolic BP (mm Hg)	90 (17)	91 (18)	89 (16)
Heart rate (bpm)	83 (20)	83 (20)	83 (20)
GCS (/15)	14 (2)	14 (2)	14 (2)
<14 (%)	174 (29)	90 (30)	84 (28)
FAST (/3)	3 (0)	3 (0)	3 (0)
=3 (%)	391 (65)	195 (65)	196 (66)
Hospital admission			
Time (min)			
RTH	24 [17,34]	23 [16,34]	25 [17,34]
RTI	55 [42,75]	55 [41,76]	56 [42,74]
Ethnicity, non-white (%)	54 (9)	23 (8)	31 (11)
Premorbid mRS>2 (%)	107 (18)	54 (18)	53 (18)
Medical history (%)			
Hypertension	355 (59)	176 (58)	179 (61)
Diabetes mellitus	125 (21)	59 (20)	66 (22)
Previous stroke	137 (23)	78 (26)	59 (20)
IHD	103 (17)	47 (16)	56 (19)
Smoking, current	90 (18)	54 (21)	36 (14)
Alcohol, >12 upw	38 (8)	17 (7)	21 (9)
Antithrombotic			
Antiplatelet therapy	139 (34)	68 (34)	71 (35)
Oral anticoagulation	38 (10)	16 (8)	22 (11)
Reperfusion (%)			
Alteplase (%)	284 (48)	150 (50)	134 (45)
Intra-arterial (%)	24 (4)	7 (2)	17 (6)
Carotid stenosis, ipsilateral (%)			
<50%	217 (79)	116 (82)	101 (77)
50%–70%	28 (10)	15 (11)	13 (10)
>70%	14 (5)	8 (6)	6 (5)
>50% bilateral	3 (1)	2 (1)	1 (1)

Data are number (%), median [IQR] or mean (SD).
AF, atrial fibrillation; BP, blood pressure; FAST, Face-Arm-Speech-Time; GCS, Glasgow Coma Scale; IHD, ischaemic heart disease; mRS, modified Rankin Scale; OTR, onset to randomisation; RTH, randomisation to hospital; RTI, randomisation to imaging; upw, units per week.

Table 2 Primary outcome and key secondary outcomes

		GTN	Sham	acOR/aOR/aDIM/aHR (95% CI)	P value
Day 90 mRS, maximum score of 6 (primary outcome)*	580	3 [2,5]	3 [2,5]	1.15 (0.85, 1.54)	0.36
Sensitivity analyses					
Unadjusted	580	3 [2,5]	3 [2,5]	0.96 (0.72, 1.28)	0.78
Mean	580	3.3 (1.9)	3.4 (1.8)	0.08 (–0.18, 0.35)	0.54
Per protocol	498	3 [2,5]	3 [2,5]	1.08 (0.79, 1.5)	0.63
Imputation	597	3 [2,5]	3 [2,5]	1.12 (0.83, 1.49)	0.46
Hospital admission					
NIHSS, maximum score of 42	550	10.4 (7.1)	10.9 (7.3)	–0.10 (–1.13, 0.92)	0.85
GCS, maximum score of 15	588	13.7 (1.9)	13.9 (1.7)	–0.27 (–0.55, 0.00)	0.054
FAST, maximum score of 3	581	2.4 (0.9)	2.4 (0.9)	0.01 (–0.11, 0.13)	0.83
OCSP, TACS (%)	586	111 (37.8)	110 (37.7)	1.05 (0.73, 1.52)	0.79
Outcomes on day 4 (or discharge)					
Death (%)	594	5 (1.7)	6 (2)	0.82 (0.24, 2.82)	0.75
Neurological deterioration (%)	413	39 (19.2)	42 (20)	1.02 (0.62, 1.69)	0.93
Headache, clinical (%)	592	28 (9.3)	18 (6.2)	1.40 (0.74, 2.67)	0.30
Hypotension, clinical (%)	593	12 (4)	9 (3.1)	1.40 (0.56, 3.49)	0.47
Hypertension, clinical (%)	593	49 (16.3)	59 (20.1)	0.71 (0.45, 1.10)	0.13
Feeding: non-oral (%)	576	79 (27.1)	90 (31.7)	0.86 (0.58, 1.27)	0.45
Patients with an SAE	597	83 (27.5)	71 (24.1)	1.26 (0.86, 1.85)	0.23
Hospital events					
Length of stay (days)	592	17.8 (27.2)	19.1 (25.8)	–0.56 (–4.77, 3.65)	0.79
Died (%)	592	37 (12.3)	39 (13.4)	1.01 (0.60, 1.70)	0.98
Died or in an institution (%)	579	120 (40.8)	118 (41.4)	1.09 (0.76, 1.56)	0.64
Day 90					
Death (%)	589	59 (19.9)	53 (18.2)	1.24 (0.85, 1.81)	0.27
Disposition, maximum score of 3†	568	1 (1.2)	1 (1.2)	1.19 (0.81, 1.74)	0.37
EQ-5D-HSUV, maximum score of 1 ‡	561	0.4 (0.4)	0.4 (0.4)	–0.01 (–0.08, 0.05)	0.71
EQ-VAS (/100)‡	515	47.7 (33.4)	47.6 (32)	–0.39 (–5.50, 4.73)	0.88
Barthel Index, maximum score of 100†	557	58.8 (44.3)	59.2 (43.8)	–2.88 (–9.24, 3.48)	0.37
TICS-M, maximum score of 100 ‡§	300	13.5 (12.5)	13.4 (11.8)	–0.65 (–2.91, 1.62)	0.58
tMMSE, maximum score of 21‡§	307	11.2 (9.9)	11.5 (9.5)	–0.91 (–2.70, 0.88)	0.32
Animal naming‡§	301	9.1 (9.6)	9.4 (9.6)	–0.95 (–2.76, 0.86)	0.30
ZDS, maximum score of 102.5§	342	66.3 (28.5)	65.4 (28.6)	2.63 (–2.61, 7.86)	0.33
Global analysis, Wei-Lachin§	300	–	–	0.00 (–0.10, 0.09)	0.92
Global analysis, Wei-Lachin with imputation	597	–	–	–0.01 (–0.09, 0.07)	0.82
Home time (days)	471	59.1 (48.3)	55.4 (45.4)	1.93 (–5.69, 9.54)	0.62

Data are number (%), mean (SD) or median [IQR]. Comparison by binary logistic regression, Cox proportional hazards regression, ordinal logistic regression or multiple linear regression, with adjustment for age, sex, premorbid mRS, FAST, pretreatment systolic BP, index event (haemorrhagic stroke, ischaemic stroke, TIA, mimic) and time to randomisation (unless stated). The effect of treatment for GTN versus sham is shown as acOR, aOR, aHR, or aDIM, with 95% CIs.
*Increased OR, that is, >1, indicates a shift to worse functional outcome.
†Disposition: home (score of 1), institution or in hospital (score of 2), died (score of 3) by day 90.
‡Death assigned: BI –5, animal naming –1, EQ-VAS –1, home time –1, tMMSE –1, TICS-M –1, EQ-5D HUS 0, GCS 2, NIHSS 43, ZDS 102.5.
§Some participants with poor outcomes or dysphasia could not answer cognition and mood questions.
acOR, adjusted common OR; aDIM, adjusted difference in means; aHR, adjusted HR; aOR, adjusted OR; BI, Barthel Index; BP, blood pressure; EQ-5D, EuroQoL-5 dimension 3 level; FAST, Face-Arm-Speech-Time; GCS, Glasgow Coma Scale; GTN, glyceryl trinitrate; HSUV, health status utility value; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OCSP, Oxfordshire community stroke project; SAE, serious adverse event; TACS, total anterior circulation syndrome; TIA, transient ischaemic attack; TICS-M, Telephone Interview Cognition Scale-Modified; t-MMSE, telephone modified Mini-Mental State Examination; VAS, Visual Analogue Scale; ZDS, Zung Depression Scale.

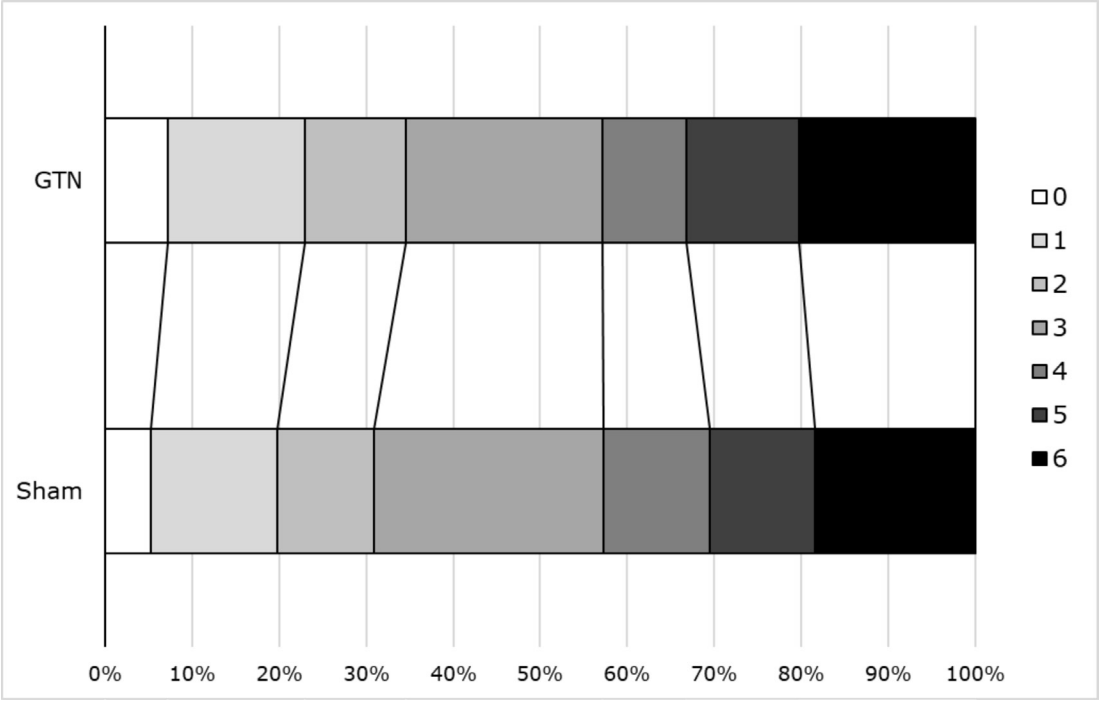

Figure 2 Shift in modified Rankin Scale in 685 participants with a final diagnosis of ischaemic stroke by treatment group—glyceryl trinitrate (GTN) versus sham. Comparison by ordinal logistic regression with adjustment for age, sex, premorbid modified Rankin Scale, face-arm-speech time test, pretreatment systolic BP and time to randomisation. The effect of treatment for GTN versus sham is shown as adjusted common OR (acOR): acOR 1.15, 95% CI 0.85 to 1.54, p=0.36. BP, blood pressure.

vs 134 (45%), p=0.30 (online supplemental table 2). Door-to-needle time did not differ between treatment groups. In contrast, fewer participants randomised to GTN underwent mechanical thrombectomy than those randomised to sham, 7 (2%) vs 17 (6%), p=0.024 (online supplemental table 2). Clinical outcomes at days 4 and 90 did not differ between GTN and sham (table 2, online supplemental figure 4). Global analysis using the Wei-Lachin test with available data (n=300), encompassing BI, EQ-5D HSUV, mRS, TICS-M, ZDS and showed no significant effect with GTN versus sham (online supplemental figure 5). This result did not alter with imputation of missing data (table 2).

Neuroimaging

Imaging on admission and days 2–4 was performed in 589 and 516 participants at a median of 2 hours and 28 hours from stroke onset, respectively (table 3). All but one scan at baseline was CT based. Baseline imaging markers of cerebral atrophy, periventricular white matter lucencies and old vascular lesions were common in isolation and cumulatively as evidence of 'brain frailty'. Acute ischaemic changes were visible in 221 (34%) participants on their admission imaging; there were no differences in location or size of ischaemia between treatment groups. ASPECTS was non-significantly lower (ie, more extensive ischaemic change) in those randomised to GTN compared with sham. CTA was available in 93 (16%) participants at baseline. Large vessel occlusions (LVOs) were seen in 49 participants and were equally distributed between GTN and sham groups. There were no differences in other CTA imaging markers between treatment groups, or on follow-up imaging on days 2–4 (table 3).

Baseline imaging markers of periventricular white matter lucencies, old vascular lesions, 'brain frailty' and SVD scores, were associated with significant unfavourable shifts in mRS at day 90. The 'brain frailty' score was also associated with an increased risk of death at 90 days; GTN did not influence these associations (online supplemental table 3).

Infarct swelling, mass effect, hyperdense artery and lower ASPECTS on baseline imaging were all associated with a shift to more death and dependency at day 90 (online supplemental table 3). Infarct swelling, mass effect and hyperdense artery on baseline imaging were also associated with an increased risk of death within 90 days. Postalteplase haemorrhagic transformation of infarction on follow-up imaging was associated with both a shift to more death and dependency and increased death at day 90. There was no interaction of treatment group with imaging features with respect to outcome.

DISCUSSION

In this prespecified subgroup analysis of the 597 patients with ischaemic stroke in the RIGHT-2 trial, we have shown that transdermal GTN did not influence clinical or radiological outcomes despite lowering BP as compared with sham. In interaction analyses there was a signal that GTN may be associated with more death and

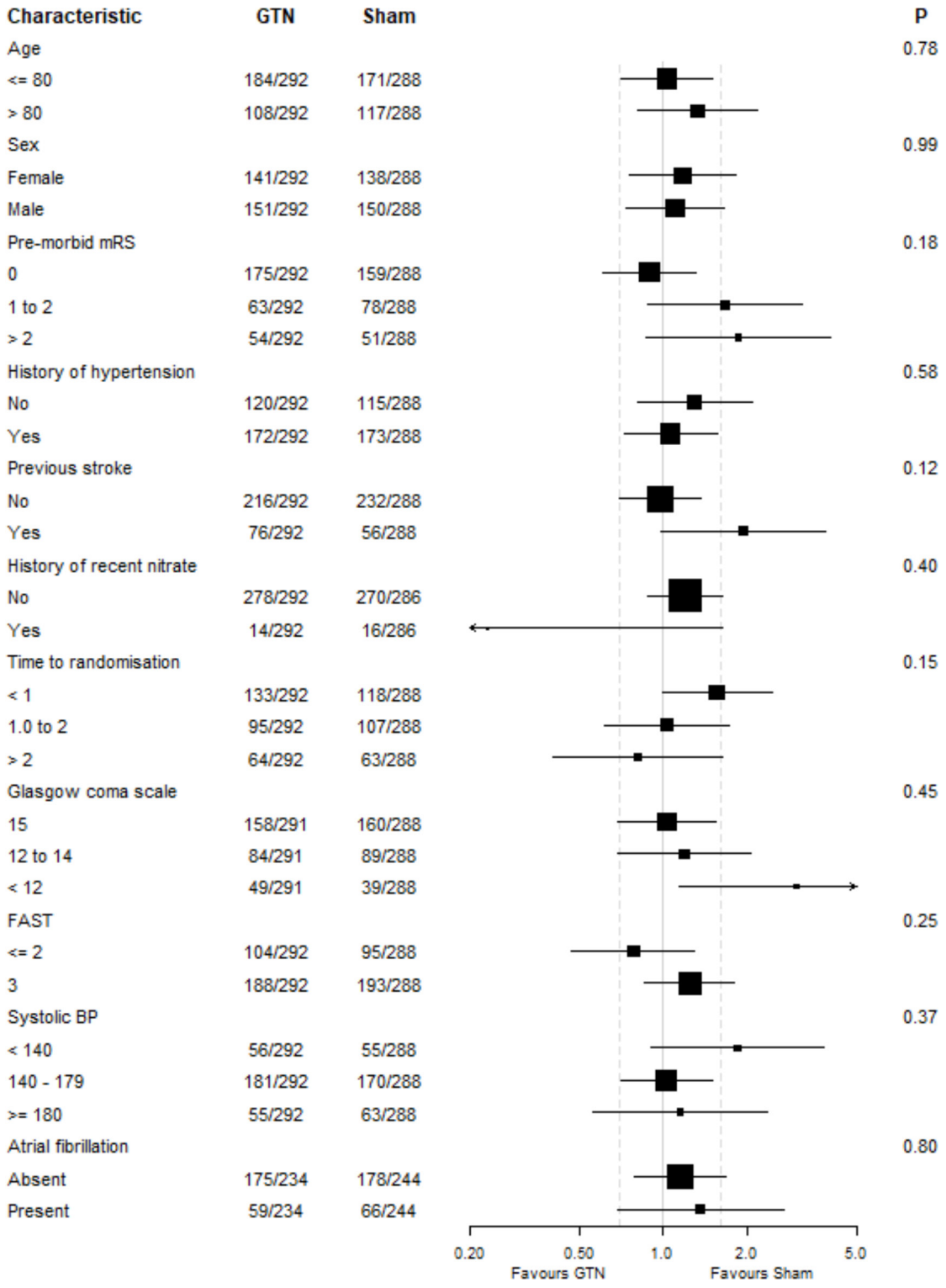

Figure 3 Forest plot showing modified Rankin Scale (mRS), analysed as ordinal outcome, in prespecified subgroups of participants with ischaemic stroke, with p value for interaction. Heterogeneity of the treatment effect on the primary outcome was assessed in prespecified subgroups by adding an interaction term to an adjusted ordinal logistic regression model as in figure 2. FAST, Face-Arm-Speech-Time; GTN, glyceryl trinitrate; BP, blood pressure.

dependency in those randomised less than 1 hour after symptom onset and in those with a higher NIHSS score, but these interactions were non-significant. Further, we have confirmed the associations between acute neuroimaging features including ASPECTS, infarct swelling, mass effect and hyperdense artery, and background neuroimaging features of 'brain frailty' and SVD (both individually and as scores) with more death and dependency at day 90 in an ultra-acute ischaemic stroke population.

Table 3 Neuroimaging findings on hospital admission (post-treatment) and at days 2–4

Outcome	Admission N	Admission GTN N=298	Admission Sham N=295	Admission acOR/aOR/aDIM (95% CI)	Admission P value	Days 2–4 N	Days 2–4 GTN N=260	Days 2–4 Sham N=259	Days 2–4 acOR/aOR/aDIM (95% CI)	Days 2–4 P value
Scan (%)										
CT	593	298 (100)	294 (>99)	–	–	519	223 (86)	226 (87)	0.88 (0.53, 1.46)	0.62
MRI	593	0 (0)	1 (<1)	–	–	519	37 (14)	33 (13)	1.14 (0.69, 1.88)	0.62
Onset to scan (hours)	589	2.1 [1.6,3.2]	2.2 [1.6,3]	1.02 (0.77 to 1.34)	0.91	516	27.4 [25.3,31.1]	28 [25.6,35.6]	0.77 (0.57, 1.04)	0.085
Normal scan*	593	3 (1)	0 (0)	–	–	519	1 (0)	0 (0)	–	–
Prestroke										
Atrophy	590	278 (94)	285 (97)	0.57 (0.26 to 1.27)	0.17					
PVL	589	141 (48)	140 (48)	1.01 (0.73 to 1.39)	0.97					
Old vascular lesion(s)	590	238 (81)	227 (77)	1.25 (0.84 to 1.86)	0.27					
'Brain frailty' score(/3)	593	2 [2,3]	2 [2,3]	1.03 (0.76 to 1.39)	0.84					
SVD score (/2)	593	1 [0,1]	1 [0,1]	1.07 (0.79 to 1.44)	0.67					
Lesion										
Location (%)										
MCA	199	96 (92)	85 (89)	1.41 (0.53 to 3.74)	0.49	384	175 (90)	169 (89)	1.14 (0.59, 2.20)	0.69
ACA	199	0 (0)	3 (3)	–	–	384	10 (5)	10 (5)	0.98 (0.40, 2.41)	0.96
PCA	199	3 (3)	7 (7)	0.37 (0.09 to 1.49)	0.16	384	11 (6)	11 (6)	0.98 (0.41, 2.31)	0.96
Lacunar	199	2 (2)	0 (0)	–		384	8 (4)	1 (1)	8.13 (1.01, 65.64)	0.049
Cerebellum or brainstem	199	2 (2)	2 (2)	0.91 (0.13 to 6.60)	0.93	384	3 (2)	7 (4)	0.41 (0.10, 1.61)	0.20
Infarct size (%)	590			1.15 (0.82 to 1.61)	0.41	516			1.07 (0.78, 1.46)	0.68
Very large		0 (0)	1 (0)				7 (3)	5 (2)		
Large		9 (3)	7 (2)				41 (16)	34 (13)		
Medium		34 (12)	29 (10)				54 (21)	64 (25)		
Small		61 (21)	58 (20)				92 (36)	85 (33)		
None visible		191 (65)	200 (68)				65 (25)	69 (27)		
Infarct expansion (%)	–	–	–	–	–	511	144 (57)	143 (56)	1.04 (0.74, 1.48)	0.81
Degree of ischaemic change (0–2)	587	0 [0,1]	0 [0,1]	1.13 (0.81 to 1.59)	0.47	507	2 [0,2]	2 [0,2]	1.03 (0.71, 1.49)	0.89
ASPECTS (/12)	191	10 [8, 11]	10 [9, 11]	0.64 (0.38 to 1.07)	0.090	355	9 [6, 10]	9 [7, 10]	0.89 (0.62, 1.29)	0.55
Infarct swelling (%)	590	68 (23)	56 (19)	1.28 (0.86 to 1.90)	0.23	518	144 (56)	149 (58)	0.92 (0.65, 1.31)	0.66
Mass effect (/6)	590	0 [0,0]	0 [0,0]	1.3 (0.87 to 1.93)	0.20	518	1 [0,2]	1 [0,2]	0.96 (0.7, 1.32)	0.80
Hyperdense artery (%)	400	78 (40)	70 (34)	1.27 (0.84 to 1.90)	0.26	437	36 (16)	33 (15)	1.10 (0.66, 1.85)	0.71
Arteries sum (0–7)	593	0 [0,0]	0 [0,0]	0.93 (0.52 to 1.66)	0.79	519	0 [0,0]	0 [0,0)	0.49 (0.09, 2.7)	0.41

Continued

Table 3 Continued

Outcome	Admission N	GTN N=298	Sham N=295	acOR/aOR/aDIM (95% CI)	P value	Days 2–4 N	GTN N=260	Sham N=259	acOR/aOR/aDIM (95% CI)	P value
Post-alteplase HTI (%)	–	–	–	–	–	281	5 (3)	11 (8)	0.38 (0.13, 1.13)	0.082
Post-thrombectomy HTI (%)	–	–	–	–	–	24	0 (0)	1 (6)	–	–
CTA										
LVO (%)										
ICA	93	8 (17)	3 (6)	3.09 (0.76 to 12.47)	0.11	5	2 (50)	0 (0)	–	–
MCA M1 (main stem)	93	7 (15)	10 (21)	0.66 (0.23 to 1.93)	0.45	5	0 (0.0)	0 (0.0)	–	–
MCA M2 (sylvian branch)	93	9 (20)	9 (19)	1.03 (0.37 to 2.87)	0.96	5	0 (0.0)	0 (0.0)	–	–
PCA	93	0 (0)	2 (4)	–	–	5	0 (0.0)	0 (0.0)	–	–
ACA	93	0 (0.0)	0 (0.0)	–	–	5	0 (0.0)	0 (0.0)	–	–
VA	93	0 (0.0)	0 (0.0)	–	–	5	0 (0.0)	0 (0.0)	–	–
BA	93	0 (0)	1 (2)	–	–	5	0 (0.0)	0 (0.0)	–	–
mTICI score (0–5)	93	0.5 (0,3)	1 (0,3)	0.84 (0.39 to 1.78)	0.64	5	0.5 (0,1.5)	0(0,0)	–	–
Mori scale (0–6)	93	0.5 (0,3)	1 (0,3)	0.8 (0.38 to 1.71)	0.57	5	0.5 (0,1.5)	0 (0,0)	–	–
Clot burden (0–10)	93	0.5 (0,7)	1 (0,8)	0.92 (0.43 to 1.95)	0.83	5	1.5 (0,5)	0 (0,0)	–	–
Arteries sum (0–7)	93	1 (0,2)	1 (0,3)	0.76 (0.36 to 1.62)	0.48	5	0.5 (0,1)	0 (0,0)	–	–
Collateral status (0–3)	93	0 (0,2)	0 (0,2)	0.82 (0.38 to 1.78)	0.62	5	0.5 (0,2)	0 (0,0)	–	–

Data are number (%), mean (SD) or median (IQR), and acOR, aOR or aDIM, with 95% CI. Comparison by binary logistic regression, Cox proportional hazards regression, ordinal logistic regression or multiple linear regression, with adjustment for age, sex, premorbid mRS, FAST, pretreatment systolic BP and time to randomisation (unless stated).
*Normal scan = no acute or chronic changes seen / no abnormality seen.
ACA, anterior cerebral artery; acOR, adjusted common OR; aDIM, adjusted difference in means; aOR, adjusted OR; ASPECTS, Alberta Stroke Programme Early CT Score; BA, basilar artery; BP, blood pressure; CTA, CT angiography; FAST, Face-Arm-Speech-Time; HTI, haemorrhagic transformation of infarct; ICA, internal carotid artery; LVO, large vessel occlusion; MCA, middle cerebral artery; mRS, modified Rankin Scale; mTICI, modified thrombolysis in cerebral infarction; PCA, posterior cerebral artery; PVL, periventricular lucencies; SVD, small vessel disease; VA, vertebral artery.

The neutral effect of transdermal GTN in ultra-acute ischaemic stroke differs from prior trials which have suggested that GTN may improve outcome when administered to patients in hospital presenting within 6 hours of symptom onset.[24 25] Although the present subgroup findings may represent chance, there are important differences between these trials that need highlighting. In contrast to RIGHT-2, the time to randomisation was 280 min in ENOS-early (the <6 hours subgroup of the ENOS trial). ENOS involved 7 days of randomised treatment as opposed to 4 days in RIGHT-2, with only 51% of participants completing all 4 days of treatment. Further, ENOS-early and RIGHT recruited participants with less premorbid dependency and comorbidity than RIGHT-2. This was also seen on imaging where baseline features of 'brain frailty' were more common in RIGHT-2 than in ENOS: atrophy 95% vs 81%; periventricular lucencies 48% vs 41% and old vascular lesion(s) 79% vs 61%.[21] Thus, RIGHT-2 may have recruited a population of more comorbid, frail and dependent patients—a population more representative of clinical practice than the majority of stroke trials to date. This is important since transdermal GTN may have different effects depending on the severity and frailty of patients. This may also explain, in part, the discrepancy seen between the neuroimaging finding of hyperdense artery sign in 148/400 (37%) participants, evidence of 49 LVOs on 93 participants with CTAs and low rates of thrombectomy (24, 4%). Other logistical factors will have influenced the rate of thrombectomy including service provision and availability.

In addition, in ultra-acute ischaemic stroke patients, we have confirmed the associations of acute neuroimaging ischaemic changes and baseline imaging markers of 'brain frailty' and SVD with poor functional outcome at 90 days as seen in other trials recruiting at later time periods.[20 21]

The strengths of our subgroup analysis include the preplanned nature and broad inclusion criteria. However, there are limitations. First, the clinical diagnosis of ischaemic stroke was not adjudicated centrally, which raises the potential for some patients to have had an alternative diagnosis. Second, CTA and perfusion imaging were performed at the discretion of the treating clinician, rather than being stipulated in the trial protocol. This may have provided useful information on whether GTN influences collateral status, penumbra and core volumes to help understand any potential underlying mechanisms of action. Third, the dependent nature of the population of patients who had an ischaemic stroke recruited may have reduced the ability to detect a treatment effect on functional outcome. To account for this, adjustment for baseline prognostic factors was built into statistical models. Last, the limited sample size means that any significant or near-significant findings may simply reflect a chance finding; only 300 participants had available data for the global analysis assessed using the Wei-Lachin test. Thus, we acknowledge that our findings presented are hypothesis-generating and require formal prospective testing.

In summary, transdermal GTN administered in the ambulance within 4 hours of symptom onset did not alter clinical or radiological outcomes in patients with ischaemic stroke. The population recruited was more dependent and frailer (clinically and radiologically) than in a prior trial subgroup of transdermal GTN given within 6 hours of symptom onset, and may account for the differences in results.

Author affiliations
[1]Stroke, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[2]Institute of Applied Health Research, University of Birmingham College of Medical and Dental Sciences, Birmingham, UK
[3]Stroke Trials Unit, Mental Health and Clinical Neurosciences, University of Nottingham, Nottingham, UK
[4]Faculty of Medicine, The George Institute for Global Health, Sydney, New South Wales, Australia
[5]The George Institute China at Peking University Health Science Center, Beijing, China
[6]Neurology, Royal Prince Alfred Hospital, Sydney Health Partners, Sydney, New South Wales, Australia
[7]Department of Neurology, King's College Hospital NHS Foundation Trust, London, UK
[8]Faculty of Health and Medical Sciences, University of Western Australia, Crawley, Western Australia, Australia
[9]East Midlands Ambulance Service NHS Trust, Nottingham, UK
[10]Stroke, Queen's Medical Centre, Nottingham University Hospitals NHS Trust, Nottingham, UK
[11]Centre for Clinical Brain Sciences, Dementia Research Institute, Univeristy of Edinburgh, Edinburgh, UK
[12]Institute of Neurology and Psychology, University of Glasgow, Glasgow, UK
[13]Bob Champion Research and Education Building, University of East Anglia, Norwich, UK
[14]Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK
[15]Department of Neurology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[16]Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK
[17]Stroke Research in Stoke, Institute for Science and Technology in Medicine, Keele University, Stoke-on-Trent, UK
[18]Department of Neurology, Oslo University Hospital, Oslo, Norway
[19]Research and Development, Norwegian Air Ambulance Foundation, Oslo, Norway
[20]Department of Neurology and Comprehensive Stroke Center, David Geffen School of Medicine, UCLA, Los Angeles, California, USA
[21]Research and Graduate Services, University of Nottingham, Nottingham, UK
[22]Community and Health Research Unit, University of Lincoln, Lincoln, UK

Twitter Jason Philip Appleton @JPAppleton, Lesley Cala @not applicable and Aloysius Niroshan Siriwardena @nsiriwardena

Acknowledgements We thank the late Professor Eivind Berge who was a member of the RIGHT-2 International Advisory Committee and contributed greatly to the trial's completion.

Contributors LJW performed the analyses. JPA interpreted the data and wrote the first draft. All authors edited the manuscript. PMB is corresponding author and guarantor for the study.

Funding British Heart Foundation (grant number CS/14/4/30972). JPA is supported by an NIHR Health and Care Research Scholarship. PMB is Stroke Association Professor of Stroke Medicine and an NIHR Senior Investigator. TR is an NIHR Senior Investigator. GM is the Stroke Association Edith Murphy Foundation Senior Clinical Lecturer (SA L-SMP 18\1000). JW is supported by the UK Dementia Research Institute which receives its funding from DRI, funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK.

Competing interests JPA is supported by an NIHR Health and Care Research Scholarship. PMB is Stroke Association Professor of Stroke Medicine and an NIHR Senior Investigator. TR is a NIHR Senior Investigator. GM is the Stroke Association Edith Murphy Foundation Senior Clinical Lecturer (SA L-SMP 18\1000). JW is supported by the UK Dementia Research Institute which receives its funding

from DRI, funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK. The remaining authors report no declarations of interest.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the trial was approved by the national research ethics committee (IRAS: 167115). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Data are available on reasonable request to the corresponding author.

ORCID iDs
Jason Philip Appleton http://orcid.org/0000-0002-2604-4410
Lisa J Woodhouse http://orcid.org/0000-0002-4472-1999
Kailash Krishnan http://orcid.org/0000-0002-6486-3783
Joanna M Wardlaw http://orcid.org/0000-0002-9812-6642
Philip M Bath http://orcid.org/0000-0003-2734-5132

REFERENCES

1 Leonardi-Bee J, Bath PMW, Phillips SJ, *et al*. Blood pressure and clinical outcomes in the International stroke trial. *Stroke* 2002;33:1315–20.
2 Willmot M, Leonardi-Bee J, Bath PMW. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension* 2004;43:18–24.
3 He J, Zhang Y, Xu T, *et al*. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. *JAMA* 2014;311:479–89.
4 Sandset EC, Bath PMW, Boysen G, *et al*. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet* 2011;377:741–50.
5 Sandset EC, Jusufovic M, Sandset PM, *et al*. Effects of blood pressure-lowering treatment in different subtypes of acute ischemic stroke. *Stroke* 2015;46:877–9.
6 Bath PM, Woodhouse L, Scutt P, *et al*. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (enos): a partial-factorial randomised controlled trial. *Lancet* 2015;385:617–28.
7 Barer DH, Cruickshank JM, Ebrahim SB, *et al*. Low dose beta blockade in acute stroke ("BEST" trial): an evaluation. *Br Med J (Clin Res Ed)* 1988;296:737–41.
8 Wahlgren NG, MacMahon DG, De Keyser J, *et al*. Intravenous nimodipine West European stroke trial (INWEST) of nimodipine in the treatment of acute ischaemic stroke. *Cerebrovasc Dis* 1994;4:204–10.
9 Anderson CS, Huang Y, Lindley RI, *et al*. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (enchanted): an international, randomised, open-label, blinded-endpoint, phase 3 trial. *Lancet* 2019;393:877–88.
10 Bath PM, Appleton JP, Krishnan K, *et al*. Blood pressure in acute stroke: to treat or not to treat: that is still the question. *Stroke* 2018;49:1784–90.
11 Rashid PA, Whitehurst A, Lawson N, *et al*. Plasma nitric oxide (nitrate/nitrite) levels in acute stroke and their relationship with severity and outcome. *J Stroke Cerebrovasc Dis* 2003;12:82–7.
12 Willmot M, Gray L, Gibson C, *et al*. A systematic review of nitric oxide donors and L-arginine in experimental stroke; effects on infarct size and cerebral blood flow. *Nitric Oxide* 2005;12:141–9.
13 Bath PM, Woodhouse L, Krishnan K, *et al*. Effect of treatment delay, stroke type, and thrombolysis on the effect of glyceryl trinitrate, a nitric oxide donor, on outcome after acute stroke: a systematic review and meta-analysis of individual patient from randomised trials. *Stroke Res Treat* 2016;2016:9706720.
14 RIGHT-2 Investigators. Prehospital transdermal glyceryl trinitrate in patients with ultra-acute presumed stroke (RIGHT-2): an ambulance-based, randomised, sham-controlled, blinded, phase 3 trial. *Lancet* 2019;393:1009–20.
15 Bath PM, Woodhouse LJ, Krishnan K, *et al*. Prehospital transdermal glyceryl trinitrate for ultra-acute intracerebral hemorrhage: data from the RIGHT-2 trial. *Stroke* 2019;50:3064–71.
16 Appleton JP, Scutt P, Dixon M, *et al*. Ambulance-delivered transdermal glyceryl trinitrate versus sham for ultra-acute stroke: rationale, design and protocol for the rapid intervention with glyceryl trinitrate in hypertensive stroke trial-2 (RIGHT-2) trial (ISRCTN26986053). *Int J Stroke* 2019;14:191–206.
17 Scutt P, Appleton JP, Dixon M, *et al*. Statistical analysis plan for the " rapid intervention with glyceryl trinitrate in hypertensive stroke trial-2 (RIGHT-2). " *Eur Stroke J* 2018;3:193–6.
18 Bath PM, Scutt P, Appleton JP, *et al*. Baseline characteristics of the 1149 patients recruited into the rapid intervention with glyceryl trinitrate in hypertensive stroke trial-2 (RIGHT-2) randomized controlled trial. *Int J Stroke* 2019;14:298–305.
19 Bruno A, Shah N, Lin C, *et al*. Improving modified Rankin scale assessment with a simplified questionnaire. *Stroke* 2010;41:1048–50.
20 IST-3 collaborative group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third international stroke trial (IST-3): secondary analysis of a randomised controlled trial. *Lancet Neurol* 2015;14:485–96.
21 Appleton JP, Woodhouse LJ, Adami A, *et al*. Imaging markers of small vessel disease and brain frailty, and outcomes in acute stroke. *Neurology* 2020;94:e439–52.
22 Lachin JM. Applications of the wei-lachin multivariate one-sided test for multiple outcomes on possibly different scales. *PLoS One* 2014;9:e108784.
23 Appleton JP, Scutt P, Sprigg N, *et al*. Hypercholesterolaemia and vascular dementia. *Clin Sci (Lond)* 2017;131:1561–78.
24 Woodhouse L, Scutt P, Krishnan K, *et al*. Effect of hyperacute administration (within 6 hours) of transdermal glyceryl trinitrate, a nitric oxide donor, on outcome after stroke: subgroup analysis of the efficacy of nitric oxide in stroke (eNOS) trial. *Stroke* 2015;46:3194–201.
25 Ankolekar S, Fuller M, Cross I, *et al*. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: the rapid intervention with glyceryl trinitrate in hypertensive stroke trial (right, ISRCTN66434824). *Stroke* 2013;44:3120–8.