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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)

Sandeep Ankolekar, MD, MRCP; Michael Fuller, DipHE; Ian Cross, DipHE; Cheryl Renton, MSc; Patrick Cox, RGN; Nikola Sprigg, MD, MRCP; A. Niroshan Siriwardena, PhD, FRCGP; Philip M. Bath, MD, FRCP

Background and Purpose—The practicalities of doing ambulance-based trials where paramedics perform all aspects of a clinical trial involving patients with ultra-acute stroke have not been assessed.

Methods—We performed a randomized controlled trial with screening, consent, randomization, and treatment performed by paramedics prior to hospitalization. Patients with probable ultra-acute stroke (<4 hours) and systolic blood pressure (SBP) >140 mm Hg were randomized to transdermal glyceryl trinitrate (GTN; 5 mg/24 hours) or none (blinding under gauze dressing) for 7 days with the first dose given by paramedics. The primary outcome was SBP at 2 hours.

Results—Of a planned 80 patients, 41 (25 GTN, 16 no GTN) were enrolled >22 months with median age [interquartile range] 79 [16] years; men 22 (54%); SBP 168 [46]; final diagnosis: stroke 33 (80%) and transient ischemic attack 3 (7%). Time to randomization was 55 [75] minutes. After treatment with GTN versus no GTN, SBP at 2 hours was 153 [31] versus 174 [27] mm Hg, respectively, with difference −18 [30] mm Hg (P=0.030). GTN improved functional outcome with a shift in the modified Rankin Scale by 1 [3] point (P=0.040). The rates of death, 4 (16%) versus 6 (38%; P=0.15), and serious adverse events, 14 (56%) versus 10 (63%; P=0.75), did not differ between GTN and no GTN.

Conclusions—Paramedics can successfully enroll patients with ultra-acute stroke into an ambulance-based trial. GTN reduces SBP at 2 hours and seems to be safe in ultra-acute stroke. A larger trial is needed to assess whether GTN improves functional outcome.

Clinical Trial Registration—URL: http://www.controlled-trials.com/ISRCTN66434824/66434824. Unique identifier: 66434824. **(*Stroke*. 2013;44:3120-3128.)**

Key Words: ambulances ■ blood pressure ■ nitroglycerin ■ prehospital ■ stroke

Ambulance administration of emergency treatment by paramedics is standard in medical emergencies, such as myocardial infarction and asthma, and can reduce time to treatment. In contrast, no stroke-specific treatment is given before hospital, largely because agents that alter hemostasis cannot be given without prior neuroimaging to distinguish ischemic stroke and primary intracerebral hemorrhage. However, potential treatments without pro- or antihemostatic activity, such as neuroprotectants and modulators of physiological disequilibrium (eg, high blood pressure [BP], hyperglycemia, pyrexia), do not need prior neuroimaging and could be delivered in the community before hospitalization.

Few studies have assessed the feasibility of ambulance administration of treatment in the ultra-acute period before hospitalization. The pilot Field Administration of Stroke Therapy–Magnesium (FAST-Mag) study gave intravenous magnesium (a potential neuroprotectant)[1] in a single-arm uncontrolled design to 20 patients in the Unites States.[2] Subsequently, the main FAST-Mag trial has recruited its planned 1700 patients and the results are awaited (http://www.fastmag.info/, accessed February 8, 2013). In FAST-Mag, paramedics screen and treat patients, but consent is performed by doctors via mobile telephone.[3,4] In a different model of healthcare delivery in the ultra-acute period, scanning, diagnosis, and treatment may be delivered at the emergency site using a Mobile Stroke Unit, an ambulance specifically equipped with computed tomography scanner, point-of-care laboratory, and medical and nursing staff.[5,6]

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From the Stroke Trials Unit, Division of Stroke, University of Nottingham, United Kingdom (S.A., C.R., P.C., N.S., P.M.B.); Department of Stroke, Nottingham University Hospitals NHS Trust, United Kingdom (S.A., N.S., P.M.B.); East Midlands Ambulance Service NHS Trust, Nottingham, United Kingdom (M.F., I.C., A.N.S.); and School of Health and Social Care, University of Lincoln, United Kingdom (A.N.S.).

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Correspondence to Philip M. Bath, MD, Division of Stroke, University of Nottingham City Hospital Campus, Hucknall Rd, Nottingham NG5 1PB, United Kingdom. E-mail philip.bath@nottingham.ac.uk

However, no study has tested the feasibility of paramedics performing all aspects of a clinical trial involving stroke patients, namely screening, consent, treatment, and measurement. This question addresses existing limitations in prehospital stroke care.[7] We assessed the feasibility of performing an ambulance-based paramedic-delivered trial in patients with ultra-acute stroke. Patients were randomized to transdermal glyceryl trinitrate (GTN, a nitric oxide donor) or no GTN. GTN was chosen because it lowers BP,[8–10] an easily measured physiological parameter in the ambulance environment, and because high BP is both common and associated with a poor outcome after stroke.[11–13]

Methods

Design

We performed a paramedic-delivered, ambulance-based, single-city prospective single-blind randomized controlled trial with blinded outcome assessment. The trial design and protocol have been published previously (http://www.right-trial.org).[14] The trial was conducted in accordance with the Declaration of Helsinki (1996) and Good Clinical Practice and had approvals from the Medicines and Health Regulatory Authority (EudraCT Number 2007-004766-40, dated January 21, 2009), local research ethics committee (reference 09/H0408/5, April 8, 2009), Nottingham University Hospitals' (NUH) National Health Service (NHS) Trust (Research and Development Department, September 30, 2009), and East Midlands Ambulance Service's (EMAS) NHS Trust (Research and Development Department, September 18, 2009). The trial was overseen by a Trial Steering Committee (P.M.B., S.A., and A.N.S.).

Study Setting

The study was conducted jointly by the University of Nottingham, EMAS, and NUH. Patients were only included if EMAS paramedics were transporting patients to the NUH comprehensive stroke service, this covering a population of 2.5 million residents of Nottingham and environs. Seventy-eight EMAS paramedics (approximately one third of all those who were available) from 12 ambulance stations in Nottingham were trained to take part in the study, this covering a population of ≈750 000 residents. Training involved meetings between the authors and paramedics, which involved presentation of the study and question-and-answer sessions.

Trial Participants

Eligible patients were recruited between February 15, 2010, and December 15, 2011, if they presented to a Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial–trained paramedic following a 999 emergency telephone call for potential stroke; were positive on the Face Arm Speech Test (score of 2 or 3)[15,16]; were within 4 hours of symptom onset (wake-up stroke defined as onset at bedtime); had systolic BP (SBP) ≥140 mm Hg (either of 2 prerandomization readings, measured using a semiautomatic sphygmomanometer); and age >40 years for men and >55 for women. Patients with definite need or contraindication for GTN, Glasgow Coma Scale ≤8, blood glucose <2.5 mmol/L, or who were nonambulatory prior to symptom onset were excluded. Paramedics called the hyperacute stroke unit at NUH prior to enrollment to confirm the presence of research staff to meet the patient on arrival.

Consent

Consent was obtained in the ambulance for randomization and the first treatment dose and measurement and then separately in hospital for subsequent treatment and follow-up. Using a single-page information sheet, potential patients were approached by a trained paramedic to take part in the study. Capacity was assessed by ensuring the patient understood their diagnosis, the aim of the trial, and treatment (method proposed by G. Ford, Newcastle).[17] If the patient agreed to take part in the study, written consent was then obtained. For patients lacking capacity, their relatives, if present, were approached to provide proxy consent. If the patient was unable to provide consent and there was no relative present, paramedics randomized patients into the trial after signing a proxy consent form on behalf of patients for the first part of the trial as witnessed by a second paramedic or ambulance technician.

Once the patient arrived in hospital, the hospital researcher discussed the trial, provided a full patient information sheet, and answered any questions before taking written informed consent. If the patient lacked capacity (eg, dysphasia, confusion, conscious level), proxy consent was sought from a relative.

Randomization and Blinding

Treatment was allocated using simple randomization with equal distribution between active and control groups and administered single-blind. Each ambulance carried 1 or 2 numbered opaque sealed envelopes in a transparent plastic blue folder that contained the paperwork related to the trial, and a second inner envelope that contained a gauze dressing (for blinding) plus or minus a single GTN patch; this inner envelope was only opened if informed consent was obtained, thereby guaranteeing allocation concealment.

Bias was reduced using multiple strategies: concealment of allocation; patient blinding to GTN (gauze dressing over patch); measurements and follow-up assessments performed blinded to treatment assignment; and analysis by intention to treat.

Trial Intervention

The study intervention was transdermal GTN patch (Nitro-Dur; Schering-Plough Ltd; 0.2 mg/h, 5 mg) or none (control). The GTN was placed on the back or shoulder and covered with gauze dressing to provide single-blinded administration. Patients randomized to the control group had a gauze dressing applied in a similar position to provide blinding of treatment to the patient.

Trial treatment was administered daily for another 6 days in hospital. Treatment was given on top of best guideline-based hospital care, including alteplase (as appropriate after acute ischemic stroke) and multimodal secondary prevention. Prestroke antihypertensive drugs were continued during the trial, according to the wishes of the responsible stroke physician.

Cohort Patients

Patients in the cohort group were selected by screening the NUH stroke unit register. Following the exclusion of non-999 admissions, consecutive patients admitted to NUH by EMAS paramedics between September 22, 2011, and January 19, 2012, who were not recruited into the RIGHT but fulfilled its inclusion/exclusion criteria were included in the cohort group. They had not been recruited to the trial either because the paramedic had not been trained in the trial procedures or because no research staff were present to receive the patient at hospital. Clinical characteristics were obtained from ambulance report forms and hospital case notes. The aim was to compare transfer timings between patients in and out with the trial.

Outcome Measures

Primary Outcome

The primary outcome was SBP (unadjusted) at 2 hours postrandomization. This outcome was chosen because it represents the sum of the trial feasibility and intervention, that is, the ability to identify, screen, recruit, randomize, treat, and take measurements in patients with ultra-acute presumed stroke in an ambulance setting. The 2-hour time reflects the time to peak effect for transdermal GTN.[18]

Other Hemodynamic Outcomes

BP and heart rate were recorded at 15 minutes (in ambulance), 120 minutes (at hospital), and on days 2 to 7. BP/heart rate derivatives were calculated as follows[19]:

Pulse pressure=SBP–diastolic BP
Rate pressure product=SBP×HR

Central BP and aortic compliance (Augmentation Index) were measured at 120 minutes using a SphygmoCor device.[9]

Clinical Outcomes

Impairment (Scandinavian Stroke Scale)[20] was measured at 2 hours and day 7. Other measurements at day 7 included recurrence, death, headache, hypotension, and neurological deterioration (defined as a 5-point reduction in the Scandinavian Stroke Scale from day 1 to day 7[20]). Final clinical functional outcomes[21] were recorded at day 90, including dependency (modified Rankin Scale [mRS]),[22] disability (Barthel Index[23]), cognition (Mini Mental State Examination),[24] mood (Zung Depression Index),[25] and quality of life (EuroQoL, as EQ-5D and EQ-VAS).[26]

Ambulance Trial Logistics Outcomes

Logistical and feasibility outcomes included recruitment rate, protocol violations, final diagnosis, and timings between ictus, paramedic arrival and departure, and arrival at hospital.

Statistical Methods

Assuming α (significance)=5%, power (1−β)=90%, and difference in SBP at 2 hours of 11 (SD 14) mm Hg (based on our previous trials with GTN),[8–10] a sample size of 68 would be needed. This was rounded ≤80 so as to allow for losses to follow-up and treatment crossovers.

Where patients died prior to an assessment, a value different from any living value was imputed into those functional measures that do not include death (death is already included in mRS, Barthel Index, and EQ-5D): Mini Mental State Examination=−1, Zung Depression Scale=102.5, EQ-VAS=−1, Scandinavian Stroke Scale=−1. This approach means that all outcomes include death, and data are available for all participants, thereby reducing attrition bias and improving statistical power.

Tabulated data are described as number (%) or median [interquartile range]. Data for each treatment group (GTN versus no GTN) were compared by intention to treat; clinical outcomes were also compared between the treatment groups in those patients whose final diagnosis was a stroke. Comparisons were performed using Fisher exact test for frequency data and Mann–Whitney *U* test (with correction for continuity and ties) for ordered categorical or continuous data. The primary analysis of mRS was performed using ordinal logistic regression as per the recommendations of the European Stroke Organization Outcomes Working Group 2011.[27,28] Number needed to treat was estimated as recently published.[29]

Results

Screening and Recruitment

Paramedic training sessions (×22) lasted 2 hours and led to the training of 78 paramedics. Of these, 30 paramedics from 10 ambulance stations screened ≥1 patient. Due to funding constraints, recruitment was stopped in December 2011 and the final follow-up was completed in March 2012.

Of 92 screened patients, 41 were recruited and randomized into the trial (Figure 1) by 23 paramedics at an average rate of 1.8 patients per month. Nineteen patients were randomized outside working hours. The principal reasons for noninclusion were: no research staff available at hospital, no trial randomization treatment pack present in the ambulance, and failure to satisfy study criteria (Figure 1). No patients were excluded due to refusal of consent.

Separately, 41 consecutive patients who fulfilled the RIGHT inclusion/exclusion criteria and were admitted to the NUH Stroke Service but not recruited into the trial were enrolled into a parallel cohort study after screening 177 patients admitted by EMAS paramedics (Figure 1).

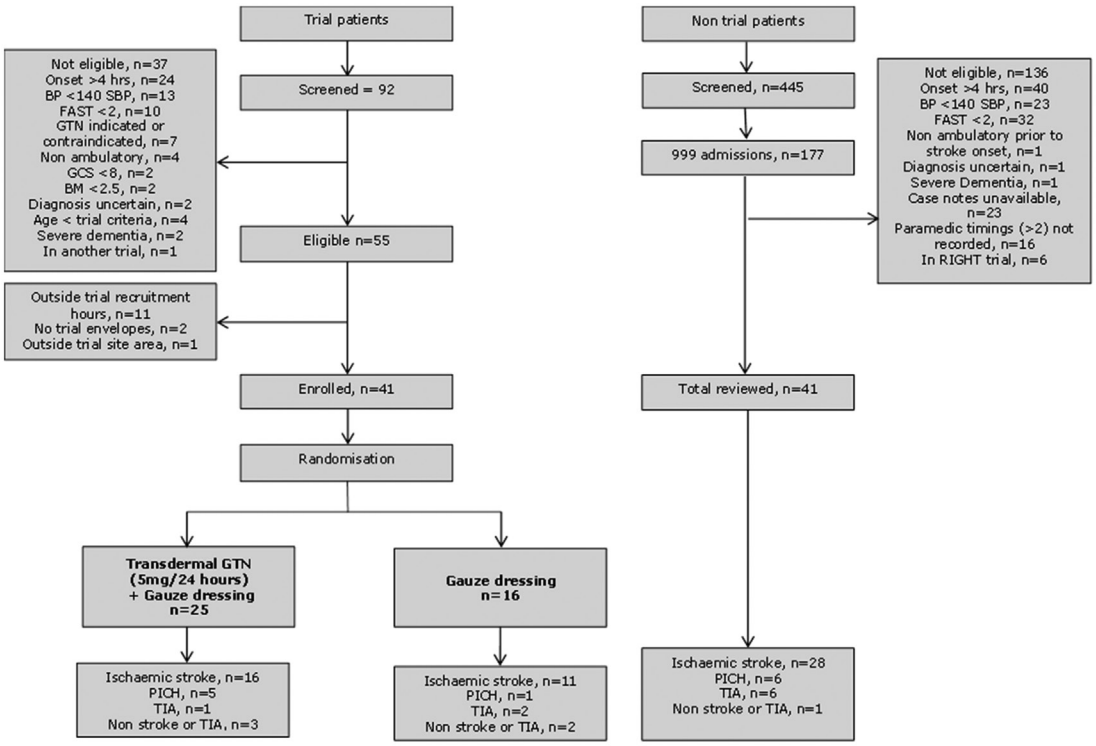

Figure 1. Trial flow chart. 999 indicates United Kingdom Emergency Number; BM, capillary glucose; BP, blood pressure; FAST, Face Arm Speech Test; GCS, Glasgow coma scale; GTN, glyceryl trinitrate; PICH, primary intracerebral hemorrhage; SBP, systolic blood pressure; and TIA, transient ischemic attack.

Patient Characteristics

Although baseline characteristics were well balanced between the treatment groups, the ratio of participants randomized to GTN versus no GTN, 25:16, was nonsignificantly different from 1:1 (P=0.16). The 41 randomized patients were older (median age 79 years) and more likely to have a diagnosis of primary intracerebral hemorrhage (15% of stroke) than in most hospital-based stroke trials (Table 1). Eight patients (20%) had a nonstroke diagnosis: transient ischemic attack (TIA; n=3), migraine (n=2), codeine-induced confusion (n=1), urinary tract infection (n=1), and alcohol-related pressure palsy (n=1). A previous diagnosis of high BP (66%) or stroke (27%) was common. Twenty-three (56.1%) patients were taking antihypertensive medications prior to admission; none of these were stopped during the treatment period and no hypotension occurred. Thrombolysis was administered to 7 (28%) participants in the GTN group and 3 (19%) receiving no GTN. When comparing baseline characteristics of trial and nontrial/cohort patients, there were no statistical differences apart from a history of ischemic heart disease that was more common in nontrial patients.

Table 1. Characteristics by Treatment Group, as Collected at Baseline in Ambulance and at Hospital Shortly After Treatment Commenced

	GTN	No GTN	All Patients	Nontrial Patients	2*P*
Ambulance					
Number of participants	25	16	41	41	
Age, y	79 [66, 84]	81 [7, 86]	79 [68, 84]	78 [72, 84]	0.69
Sex, men (%)	15 (60.0)	7 (43.8)	22 (53.7)	23 (56.1)	1.00
Risk factors (%)					
Hypertension	16 (64.0)	11 (68.8)	27 (65.9)	26 (65.0)	1.00
Hyperlipidaemia	10 (40.0)	4 (25.0)	14 (34.1)	16 (39.0)	0.82
Diabetes mellitus	2 (8.0)	2 (12.5)	4 (9.8)	5 (12.5)	1.00
Atrial fibrillation	5 (20.0)	3 (18.8)	8 (19.5)	8 (19.5)	1.00
Previous stroke	8 (32.0)	3 (18.8)	11 (26.8)	10 (24.4)	1.00
Ischemic heart disease	8 (32.0)	0	2 (4.9)	8 (20.0)	0.048
Previous antihypertensives (%)	15 (60.0)	8 (50.0)	23 (56.1)	19 (46.3)	0.51
Previous antiplatelets (%)	12 (48.0)	5 (31.3)	17 (41.5)	16 (39.0)	1.00
Premorbid mRS (/6)	1 [0, 2]	1 [0, 2]	1 [0, 2]	N/C	…
FAST score (/3)	3 [2, 3]	3 [2, 3]	3 [2, 3]	3 [2, 3]	0.32
Systolic BP, mm Hg*	166 [147, 190]	169 [147, 214]	168 [147, 193]	164 [149, 191]	0.94
Diastolic BP, mm Hg*	92 [82, 107]	93 [73, 103]	93 [80, 105]	96 [86, 106]	0.29
Systolic BP ≤185 mm Hg (%)	17 (68)	10 (63)	27 (66)	28 (73.2)	1.00
Heart rate, bpm	85 [68, 96]	76 [66, 88]	81 [68, 93]	78 [72, 88]	0.77
Time to randomization, min	54 [45, 120]	65 [36, 99]	55 [45, 120]	N/R	…
Hospital					
Scandinavian Stroke Scale (/58)	38 [28, 47]	38 [16, 55]	38 [26, 51]	N/C	…
Stroke syndrome (%)					
TACS	9 (36.0)	6 (37.5)	15 (36.6)	18 (43.9)	…
PACS	9 (36.0)	4 (25.0)	13 (31.7)	10 (24.39)	…
LACS	3 (12.0)	4 (25.0)	7 (17.1)	5 (12.2)	…
POCS	1 (4.0)	0	1 (2.4)	2 (4.9)	…
Final diagnosis (%)					
Ischemic stroke	16 (64.0)	11 (68.8)	27 (65.9)	28 (68.3)	0.52
Primary hemorrhage	5 (20.0)	1 (6.3)	6 (14.6)	5 (12.2)	…
Transient ischemic attack	1 (4.0)	2 (12.5)	3 (7.3)	6 (14.6)	…
Nonstroke	3 (12.0)	2 (12.5)	5 (12.2)	2 (4.88)	…
Thrombolysis					
Alteplase (%)	7 (28.0)	3 (18.8)	10 (24.4)	14 (34.1)	0.33
Time, door-to-needle, min	53 [51, 105; n=7]	83 [61, 83; n=3]	67 [53, 83; n=10]	N/C	…

Data are given as number (%) or median [interquartile range]. Comparison between trial and nontrial patients using Fisher exact test or Mann–Whitney *U* test. BP indicates blood pressure; GTN, glyceryl trinitrate; FAST, Face Arm Speech Test; LACS, lacunar syndrome; mRS, modified Rankin Scale; N/C, not collected; N/R, not relevant; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; and TACS, total anterior circulation syndrome.

*Mean of 2 measurements (not all patients have 2 measurements).

Consent

For the prehospital phase, consent was obtained directly from 9 (22%) patients, proxy consent from a relative in 21 (51%) patients, and proxy consent from a paramedic in the remaining 11 (27%) patients. Patients needing proxy consent to enter the trial were older, had more severe stroke, and a worse outcome than those giving their own consent (Table I in the online-only Data Supplement).There were no refusals when hospital consent/proxy consent was sought to continue the patient in the trial.

Timings

There were no differences in any of the time intervals measured when comparing patients in the trial and parallel nontrial cohort (Table II in the online-only Data Supplement). Importantly, time from paramedic review to leaving the scene did not differ: trial patients 32 minutes versus nontrial 26 minutes, with difference 4 minutes (95% confidence interval, −3 to 9; P=0.23). The median time to randomization from stroke onset was 55 minutes (Table 1) with 32 (78%) patients randomized within 120 minutes from stroke onset. Clinical assessments at the protocol-specified times of 15 minutes (in ambulance) and 120 minutes (in hospital) post randomization were performed at a median of 15 and 134 minutes, respectively (Table II in the online-only Data Supplement).

Hemodynamic Effects

As compared with no GTN, GTN lowered peripheral SBP significantly by 21 mm Hg at 15 minutes postrandomization and by 18 mm Hg at 2 hours (primary outcome; Table 2). GTN also reduced central SBP, pulse pressure, and Augmentation Index at 2 hours, but had no effect on heart rate at 15 minutes or 2 hours. During the 7 days of treatment, BP fell in both treatment groups.

Clinical Outcomes

At day 7 (or discharge), the treatment groups did not differ in levels of impairment (Scandinavian Stroke Scale) or the proportions of participants who had neurological deterioration, a serious adverse event, or who died (Table 3). Headache and hypotension tended to be more common with GTN.

GTN was associated with an improved functional outcome at day 90, assessed using the mRS and manifest as a shift to independence/less dependency (difference in mRS, 1.0; numbers needed to treat, 3; Table 3; Figure 2). Using univariate analyses of potential correlates of functional

Table 2. Effect of GTN Versus No GTN on Hemodynamic Measures at 15 Minutes and 2 Hours

	GTN		No GTN		Difference,	
	N	Median [IQR]	n	Median [IQR]	Median (95% CI)	2*P*
Participants	25		16			
15 min (ambulance)						
Blood pressure, mm Hg						
Peripheral						
Systolic*	25	153 [143, 173]	16	180 [151, 198]	−21 (−39, 1)	0.049
Diastolic*	25	92 [82, 101]	16	98 [85, 113]	−6 (−18, 7)	0.36
Pulse pressure	25	66 [52, 75]	16	81 [70, 99]	−16 (−30, −3)	0.009
SBP ≤185 mm Hg (%)	25	20 (80.0)	16	10 (63.0)	...	0.29
Heart rate, bpm*	25	78 [66, 92]	16	75 [66, 95]	1 (−12, 12)	0.93
2 h (hospital)						
Blood pressure, mm Hg						
Peripheral						
Systolic*	25	153 [139, 170]	16	174 [156, 183]	−18 (−32, −2)	0.030
Diastolic*	25	85 [77, 93]	16	82 [75, 91]	3 (−7, 12)	0.51
Pulse pressure	25	68 [61, 84]	16	93 [80, 101]	−20 (−33, −9)	0.002
SBP ≤185 mm Hg (%)	25	22 (88.0)	16	14 (87.5)	…	1.00
Central						
Systolic	23	134 [123, 140]	12	162 [146, 167]	−27 (−40, −7)	0.011
Diastolic	23	85 [76, 94]	12	84 [79, 89]	1 (−8, 10)	0.78
Pulse pressure	23	44 [37, 64]	12	78 [68, 87]	−30 (−41, −15)	0.002
Heart rate, bpm*	25	78 [65, 88]	16	71 [63, 81]	5 (−7, 16)	0.44
Rate pressure product	25	11571 [10223, 15569]	16	12529 [10171, 14549]	−666 (−2563, 1809)	0.64
Augmentation Index	23	128 [114, 143]	12	152 [144, 167]	−25 (−39, −10)	0.003
Buckberg Index	23	128 [110, 164]	12	131 [110, 150]	4 (−18, 31)	0.73

Data are frequency (%) or median [IQR]; comparison by Fisher exact test or Mann–Whitney *U* test. BP indicates blood pressure; CI, confidence interval; FAST, Face Arm Speech Test; GTN, glyceryl trinitrate; IQR, interquartile range; mRS, modified Rankin Scale; N/C, not collected; N/R, not relevant; and SBP, systolic blood pressure.

*Mean of 2 measurements (not all patients have 2 measurements).

outcome, only age was significantly related to mRS. In a post hoc analysis, when age was partialed out, mRS remained related to GTN (partial correlation coefficient, −0.296; *P*=0.06). When considering the mRS as a binary outcome, poor outcomes tended to be less common with GTN: mRS >1; GTN 18 (72.0%) versus no GTN 15 (93.8%; *P*=0.12; Table 3). In patients with a final diagnosis of stroke, the effect of GTN on mRS shift remained significant (n=31; *P*=0.017). Length of hospital stay did not differ between the treatment groups.

One or more serious adverse events occurred in 24 participants during the 90 days of treatment and follow-up with no difference between GTN and no GTN: 14 (56%) and 10 (63%), respectively (Table 3). Eleven protocol violations occurred (Table 4), these relating to failures to follow inclusion–exclusion criteria and failures in consent. One serious breach of good clinical practice occurred when some study drug envelopes were mislaid. Following reporting to the Medicines and Health Regulatory Authority and a full investigation, trial envelopes were replaced with large plastic packs to make them more obvious; no further drug was mislaid after this.

Discussion

The RIGHT was designed to assess the feasibility of performing an ambulance-based stroke trial in the United Kingdom. The study shows that paramedics were successful in identifying people with ultra-acute potential stroke, screening them against trial inclusion/exclusion criteria, taking informed consent or proxy consent, enrolling, randomizing, treating, and performing study-related assessments. This was reflected, overall, by recruitment of 41 patients and the demonstration that GTN reduced SBP at 2 hours post-treatment, the trial's primary outcome. The study aimed to recruit 80 patients from the Nottingham environs >2 years but managed just over half this (41; 51%), whereas the same number of cohort patients could be recruited in just <4 months. Several reasons could account for this difference: insufficient number of paramedics participating in the trial (becase each paramedic only sees 2–3 stroke patients per month, of whom many will be ineligible), lack of 24-hour research staff cover in the hospital, and paramedic concern that patients should be taken to hospital rapidly for potential thrombolysis. To address a lower-than-anticipated recruitment rate, additional paramedics were recruited and trained and update sessions organized for the original paramedics. Future trials will need to involve and train the

Table 3. Effect of GTN Versus No GTN on Clinical Outcomes in All Patients, and Those With a Final Diagnosis of Stroke, at Days 7 and 90

	All Participants				Stroke Only			
	GTN	No GTN	Difference	2*P*	GTN	No GTN	Difference	2*P*
Participant	25	16			21	12		
Day 7								
SSS (/58)	51 [26, 56]	39 [3, 58]	2 (−5, 21)	0.62	51 [26, 56]	29 [2, 42]	17 (−2, 34)	0.10
Death (%)	2 (8.0)	1 (6.3)		1.00	2 (9.5)	1 (8.3)		1.00
SAE (%)	11 (44.0)	9 (56.3)		0.53	10 (47.6)	7 (58.3)		0.72
Headache (%)	8 (32.0)	1 (6.3)		0.07	6 (28.6)	0		0.06
Hypotension (%)	2 (8.0)	0		0.51	1 (4.8)	0		1.00
Death or deterioration (%)	6 (24.0)	5 (31.3)		0.72	6 (29.0)	5 (42)		0.47
Recurrence (%)	2 (8.0)	2 (12.5)		0.64	2 (9.5)	2 (16.7)		0.61
Day 90								
mRS	3 [1, 4]	5 [3, 6]	−1 (−3, 0)	0.040	3 [2, 5]	5 [4, 6]	−2 (−3, 0)	0.017
mRS >2 (%)	13 (52.0)	12 (75.0)		0.20	11 (52.4)	11 (91.7)		0.03
Death (%)	4 (16.0)	6 (37.5)		0.15	4 (19.0)	5 (41.7)		0.23
SAE (%)	14 (56.0)	10 (63)		0.75	13 (61.9)	7 (58.3)		1.00
Hospital length of stay, d	9 [5, 58]	50 [3, 110]	−2.5 (−52, 4)	0.33	12 [6, 58]	58 [21, 110]	31 (−59, 1)	0.16
Death or institutionalization (%)	8 (32.0)	8 (50.0)		0.33	7 (33.0)	7 (58.0)		0.27
Barthel Index	85 [15, 100]	15 [−5, 85]	15 (0, 75)	0.11	85 [18, 98]	8 [−5, 73]	30 (0, 85)	0.04
MMSE	25 [8, 27]	11 [−1, 26]	2 (0, 19)	0.07	27 [8, 27]	7 [−1, 24]	7 (0, 22)	0.02
ZDS	21 [19, 29]	27 [20, 103]	−3 (−21, 1)	0.19	22 [19, 32]	30 [21, 103]	−3.5 (−75, 1)	0.19
EQ-5D	0.5 [0.2, 0.7]	0.2 [0.0, 0.4]	0.5 (0.2, 0.7)	0.09	0.5 [0.1, 0.7]	0.1 [0.0, 0.4]	0.2 (0.0, 0.6)	0.08
EQ-VAS	53 [20, 80]	45 [−1, 75]	5 (−10, 40)	0.48	50 [5, 80]	33 [−1, 78]	5 (−20, 46)	0.59
Protocol violation (%)	5 (20.0)	5 (31.3)		1.00	4 (19.0)	5 (41.7)		0.64

Data are frequency (%) or median [interquartile range] with 95% confidence intervals; comparison by Fisher exact test or Mann–Whitney *U* test (with Hodges Lehmann estimation of confidence intervals). Participants who died were assigned the following values: SSS=−1, mRS=6, BI=−5, MMSE=−1, ZDS=102.5, EQ-5D=0, EQ-VAS=1, length of stay=110. MMSE and EQ-VAS are missing for 2 patients where the carer answered the questions. MMSE, ZDS, BI, EQ-5D, and EQ-VAS are missing for 1 participant where only the mRS was obtained. BI indicates Barthel Index; EQ-5D, Euro quality of life; EQ-VAS, EuroQol Visual Analogue Scale; GTN, glyceryl trinitrate; MMSE, Mini Mental State Examination; mRS, modified Rankin Scale; SAE, serious adverse event; SSS, Scandinavian Stroke Scale; and ZDS, Zung Depression Scale.

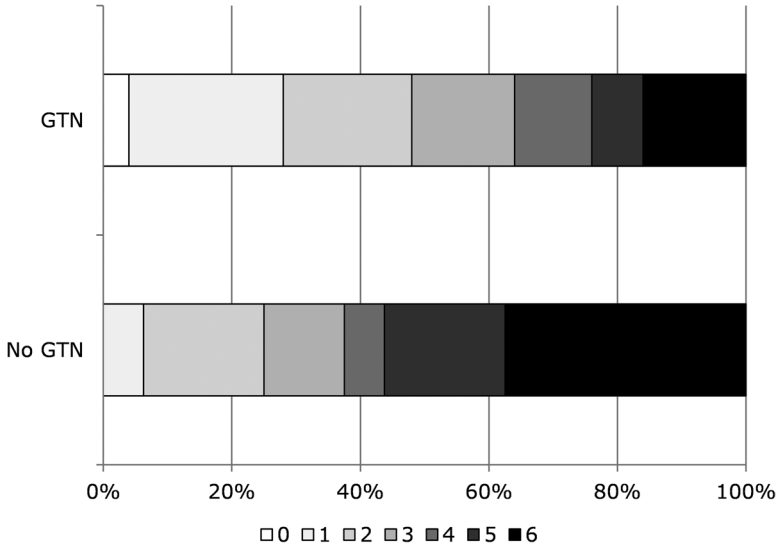

Figure 2. Modified Rankin Scale at 90 days in patients randomized to glyceryl trinitrate (GTN; n=25) versus non-GTN (n=16) groups. Comparison by Mann–Whitney *U* test, *P*=0.040.

majority of paramedics in each participating ambulance station to address these issues.

The median time from stroke onset to randomization was 55 minutes, which is quicker than that seen in the FAST-Mag pilot trial of field administration of magnesium (100 minutes from onset to start of treatment)[2] and shorter than previous trials involving agents that lower BP, such as Intravenous Nimodipine West European Stroke Trial (INWEST; nimodipine, 5.5 hours), Intravenous Magnesium Efficacy in Stroke (IMAGES; magnesium, 7 hours), Scandinavian Candesartan Acute Stroke Trial (SCAST; 18 hours), and Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS; 17–20 hours).[1,30–32] The efficacy of acute stroke treatments can be highly time-dependent, as seen with alteplase,[33] and because existing evidence for the effect of BP lowering on functional outcome has yet to find benefit,[31,34] it is now vital to test the effect of BP lowering in the ultra-acute phase after stroke onset, as done here.

Table 4. Protocol Violations

Violation	Comment	Number of Patients
Prehospital phase		
Not ambulatory prior to stroke	Prestroke mRS=4	3
Already in another trial	In ENOS trial of GTN[21] from recent stroke	1
Randomization >4 h	Wake-up strokes	3
Paramedic did not inform hospital research staff that patient was in trial		1
No witness signature from a colleague when paramedic gave proxy consent		2
Hospital phase		
Failure to obtain continuing consent for the hospital phase of the trial	Written information provided and verbal consent taken from patient's relative, but rapid patient deterioration precluded obtaining written informed consent	1

Some patients had >1 violation. ENOS indicates Efficacy of Nitric Oxide in Stroke; GTN, glyceryl trinitrate; and mRS, modified Rankin Scale.

The diagnosis of stroke or TIA (because the 2 may not be distinguishable at 1 hour postevent) made by the paramedic, in the context of an emergency 999 call for stroke and a positive Face Arm Speech Test, was confirmed by the admitting team in 88% of patients, a comparable figure to that seen in the original validity studies for the Face Arm Speech Test (78%).[16] However, paramedics had to contact the NUH hyperacute stroke unit before enrollment so that it is possible that this second opinion improved the diagnostic accuracy. Future trials will have to train paramedics to achieve an even higher diagnostic accuracy, as seen in the FAST-Mag pilot[2] where the diagnosis of stroke/TIA was 100%. Notably, the Los Angeles Prehospital Stroke Screen, rather than Face Arm Speech Test, was used in that study and a trial medic talked to each patient by telephone before enrollment, thereby providing expert triage. Nevertheless, FAST-Mag pilot and RIGHT are both small studies, and large trials are now needed to confirm that a stroke–TIA predominant population may be enrolled by paramedics, as is being tested in the now completed FAST-Mag trial in the United States.

Informed consent or proxy consent was obtained for all patients. Using a novel approach, paramedics (witnessed by the accompanying ambulance technician) were trained to give proxy consent, with this occurring in 27% of patients. Unsurprisingly, patients requiring proxy consent (either by relative or paramedic) had more severe stroke and a worse outcome than those able to give their own consent. Future ambulance-based trials will need to use proxy consent if they are to include patients with a range of clinical presentations, including those with severe stroke, dysphasia, or reduced consciousness; indeed it is the right of such patients to be offered ultra-acute treatment in the field. In the FAST-Mag pilot study, the investigator physician took informed consent over the telephone from the patient or their relative.[2] However, this is a complex, time-consuming, and expensive process, and allowing paramedics to give proxy consent should reduce time to consent and the necessity of having research medical staff available 24 hours per day.

Ten patients had ≥1 protocol violations; the rate of some of these violations (premorbid dependency, stroke onset >4 hours) could be reduced in future studies with more regular training/retraining of paramedics on the trial protocol. This is important because each participating paramedic may only see 1 or 2 patients with likely stroke each month. However, organizing training sessions was a challenge in RIGHT due to paramedic shift working patterns.

A key secondary aim of the trial was to assess the safety and hemodynamic effects of GTN in the ultra-acute phase of stroke. GTN reduced peripheral SBP by 21 and 18 mm Hg at 15 and 120 minutes, respectively, as compared with no GTN; these reductions are comparable to those seen in earlier studies in patients with recent stroke.[8–10] Similarly, GTN reduced central SBP, which most closely approximates to the pressure the brain is perfused at, and Augmentation Index, that is, it improved vascular compliance, as also seen previously.[9] The failure to see an effect on diastolic BP may be due to the small size of the trial because antihypertensive drugs have a larger effect on SBP than diastolic BP. Patients receiving GTN had a significantly better outcome assessed using the mRS, an unexpected finding in view of the small size of the trial. A trend toward a lower death rate, and higher Barthel Index, Mini Mental State Examination, and EQ-5D, was also seen with GTN, and there were no trends against GTN in outcomes such as deterioration or serious adverse event rates. Although there were no significant differences at baseline between the treatment groups, the small sample size precluded formal covariate adjustment of mRS (although this is recommended for larger trials).[35] Patients with ischemic stroke and randomized to GTN were more likely (all trends) to have a SBP ≤185 mm Hg at 15 minutes, receive thrombolysis, and have a quicker stroke treatment time. Although this could reflect chance, it is plausible that GTN might prime patients for thrombolysis by allowing more of them to have a SBP within the target range and, therefore, more to be treated and more quickly.

The finding of improved outcome with GTN requires discussion as to potential reasons. In the context of a very small trial, chance must be the most likely explanation. Although there were no obvious imbalances in measured baseline prognostic factors, an imbalance in ≥1 unmeasured factors is a distinct possibility. Supporting this is the poor functional outcome (median mRS, 5) in patients randomized to no GTN, despite apparent baseline matching. However, chance is unlikely to be the only explanation because the effect of GTN was most apparent in patients with a definite stroke (ie, once patients with TIA or mimic were excluded; Table 3), and a number of potential mechanisms are possible. First, GTN lowered SBP by ≈20 mm Hg and so could improve outcome because high BP is associated independently with a poor outcome.[11–13] Second, GTN could prime patients for thrombolysis by increasing the proportion who have a SBP <185 mm Hg; trends toward more patients receiving alteplase, and them having it earlier, were all apparent in the present trial. Increased use of alteplase in the GTN group would in itself also tend to improve outcome. Third, GTN could be acting as a neuroprotectant because nitric oxide donors exhibit this property in experimental stroke. Fourth, GTN might improve reperfusion through opening collateral pial arteries; nitric oxide is a key mediator of pial arterial tone.[36] Fifth, GTN might reduce blood sludging by opening up microvessels. In the future, GTN might even prime for intra-arterial therapy by reducing vasospasm. Accepting that much of the treatment effect size seen in RIGHT is likely to reflect chance, a smaller effect (of about one quarter) would still be worthwhile in view of the ready availability of GTN, its ease of administration, and its low cost (£6 per patient).

The main caveats with the RIGHT trial are its small size and single-site nature. Clearly, the effect of GTN on mRS should be interpreted with extreme caution as the study was not powered to assess functional outcome. Nevertheless, ambulance-based stroke trials seem to be feasible, at least in the United Kingdom prehospital environment, and paramedics are able to screen, consent, randomize, treat, and measure outcomes in patients with ultra-acute presumed stroke. Such trials would allow the ultra-acute testing of neuroprotection and interventions for altering physiological disequilibrium. GTN lowered BP and appeared to be safe. The planned multicenter RIGHT-2 trial will address these caveats and further examine the feasibility of an ambulance-based trial when run across multiple ambulance services, as well as the safety and efficacy of GTN (including by stroke type: ischemic versus hemorrhagic) and mechanisms by which it might work when administered in the ultra-acute period after stroke.

Conclusions

Paramedics can successfully enroll patients with ultra-acute stroke into an ambulance-based trial. GTN reduces SBP at 2 hours and seems to be safe in ultra-acute stroke. A larger trial is needed to assess whether GTN improves functional outcome.

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References

1. Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. *Lancet*. 2004;363:439–445.
2. Saver JL, Kidwell C, Eckstein M, Starkman S; FAST-MAG Pilot Trial Investigators. Prehospital neuroprotective therapy for acute stroke: results of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) pilot trial. *Stroke*. 2004;35:e106–e108.
3. Sanossian N, Starkman S, Liebeskind DS, Ali LK, Restrepo L, Hamilton S, et al; FAST-MAG Trial Investigators. Simultaneous ring voice-over-Internet phone system enables rapid physician elicitation of explicit informed consent in prehospital stroke treatment trials. *Cerebrovasc Dis*. 2009;28:539–544.
4. Sanossian N, Starkman S, Eckstein M, Stratton S, Pratt F, Conwit R, et al; FAST-MAG Trial Investigators. Intercontinental elicitation of informed consent for enrollment in stroke research. *Cerebrovasc Dis*. 2010;30:323–324.
5. Walter S, Kostopoulos P, Haass A, Keller I, Lesmeister M, Schlechtriemen T, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. *Lancet Neurol*. 2012;11:397–404.
6. Ebinger M, Rozanski M, Waldschmidt C, Weber J, Wendt M, Winter B, et al; STEMO-Consortium. PHANTOM-S: the prehospital acute neurological therapy and optimization of medical care in stroke patients—study. *Int J Stroke*. 2012;7:348–353.
7. Meairs S, Wahlgren N. Summary of stroke research priorities. The European Commission Stroke. Workshop, Brussels, Belgium; 2005.
8. Bath PM, Pathansali R, Iddenden R, Bath FJ. The effect of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure and platelet function in acute stroke. *Cerebrovasc Dis*. 2001;11:265–272.
9. Rashid P, Weaver C, Leonardi-Bee JA, Fletcher S, Bath FJ, Bath PMW. The effects of transdermal glyceryl trinitrate, a nitric oxide donor on blood pressure, cerebral and cardiac haemodynamics and plasma nitric oxide levels in acute stroke. *J Stroke Cerebrovasc Dis*. 2003;13:143–151.
10. Willmot M, Ghadami A, Whysall B, Clarke W, Wardlaw J, Bath PM. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. *Hypertension*. 2006;47:1209–1215.
11. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA; IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke*. 2002;33:1315–1320.
12. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension*. 2004;43:18–24.
13. Sprigg N, Gray LJ, Bath PMW, Boysen G, De Deyn PP, Friis P, et al. Relationship between outcome and baseline blood pressure and other haemodynamic mreasures in acute ischaemic stroke: data from the taist trial. *J Hypertension*. 2006;24:1413–1417.
14. Ankolekar S, Sare G, Geeganage C, Fuller M, Stokes L, Sprigg N, et al. Determining the feasibility of ambulance-based randomised controlled trials in patients with ultra-acute stroke: study protocol for the "Rapid Intervention with GTN in Hypertensive Stroke Trial" (RIGHT, ISRCTN66434824). *Stroke Res Treat*. 2012;2012:385753.
15. Harbison J, Massey A, Barnett L, Hodge D, Ford GA. Rapid ambulance protocol for acute stroke. *Lancet*. 1999;353:1935.
16. Nor AM, McAllister C, Louw SJ, Dyker AG, Davis M, Jenkinson D, et al. Agreement between ambulance paramedic- and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients. *Stroke*. 2004;35:1355–1359.
17. Shaw L, Price C, McLure S, Howel D, McColl E, Ford GA. Paramedic Initiated Lisinopril For Acute Stroke Treatment (PIL-FAST): study protocol for a pilot randomised controlled trial. *Trials*. 2011;12:152.
18. Wolff M, Luckow V. In vitro and in vivo-release of nitroglycerin from a new transdermal therapeutic system. *Pharmaceut Res*. 1985;1:23–29.
19. Gray LJ, Sprigg N, Rashid PA, Willmot M, Bath PMW. Effect of nitric oxide donors on blood pressure and pulse pressure in acute and sub-actue stroke. *J Stroke Cerebrovasc Dis*. 2006;15:245–249.
20. Bath PM, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, et al. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. *Lancet*. 2001;358:702–710.
21. The ENOS Trial Investigators. Glyceryl trinitrate vs. control, and continuing vs. stopping temporarily prior antihypertensive therapy, in acute stroke: rationale and design of the Efficacy of Nitric Oxide in Stroke (ENOS) trial (isrctn99414122). *Int J Stroke*. 2006;1:245–249.
22. Lees KR, Bath PMW, Schellinger PD, Kerr DM, Fulton R, Hacke W, et al. Contemporary outcome measures in acute stroke research: choice of primary outcome measure. *Stroke*. 2012;43:1163–1170.
23. Wade DT. *Measurement in Neurological Rehabilitation*. Oxford: Oxford University Press; 1992.
24. Schellinger PD, Bath PMW, Lees K, Bornstein NM, Uriel E, Eisert W, et al. Assessment of addtional endpoints relevant to the benefit of patients after stroke—what, when, where, in whom. *Int J Stroke*. 2012;7:227–230.
25. Zung WW. A Self-Rating Depression Scale. *Arch Gen Psychiatry*. 1965;12:63–70.
26. Euroqol Group. Euroqol—a new facility for the measurement of health-related quality of life. The euroqol group. *Health Policy*. 1990;16:199–208.
27. The Optimising Analysis of Stroke Trials (OAST) Collaboration. Can we improve the statistical analysis of stroke trials? Statistical re-analysis of functional outcomes in stroke trials. *Stroke*. 2007;38:1911–1915.
28. Bath PM, Lees KR, Schellinger PD, Altman H, Bland M, Hogg C, et al. Statistical analysis of the primary outcome in acute stroke trials. *Stroke*. 2012;43:1171–1178.
29. Optimising the Analysis of Stroke Trials Collaboration With the Writing Committee, Bath P, Hogg C, Tracy M, Pocock S. Calculation of numbers-needed-to-treat in parallel group trials assessing ordinal outcomes: case examples from acute stroke and stroke prevention. *Int J Stroke*. 2011;6:472–479.
30. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol*. 2009;8:48–56.
31. Sandset EC, Bath PM, Boysen G, Jatuzis D, Korv J, Luders S, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled double-blind trial. *Lancet*. 2011;377:741–750.
32. Wahlgren NG, MacMahon DG, de Keyser J, Indredavik B, Ryman T, INWEST Study Group. Intravenous Nimodipine West European Stroke Trial (INWEST) of nimodipine in the treatment of acute ischaemic stroke. *Cerebrovasc Dis*. 1994;4:204–210.
33. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, et al; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375:1695–1703.
34. Geeganage CM, Bath PM. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke: a metaregression. *Hypertension*. 2009;54:775–781.
35. The Optimising Analysis of Stroke Trials (OAST) Collaboration. Should stroke trials adjust functional outcome for baseline prognostic factors? *Stroke*. 2009;40:888–894.
36. Morikawa E, Rosenblatt S, Moskowitz MA. L-arginine dilates rat pial arterioles by nitric oxide-dependent mechanisms and increases blood flow during focal cerebral ischaemia. *Br J Pharmacol*. 1992;107:905–907.

SUPPLEMENTAL MATERIAL

Supplement Table 1. Comparison of patient characteristics between those giving consent or requiring proxy consent from a relative or paramedic. Data are median [interquartile range] or frequency (%); overall comparison by non-parametric ANOVA or chi-squared test.

	Consent	Proxy consent Relative	Proxy consent Paramedic	p non parametric ANOVA or χ^2
Number (%)	9 (22.0)	21 (51.2)	11 (26.8)	
In ambulance				
GTN group (%)	4 (44.4)	15 (71.4)	6 (54.5)	0.34
Age (years)	74 [61, 77]	83 [79, 86]	76 [66, 86]	0.03
Sex, male (%)	5 (55.6)	12 (57.1)	5 (45.5)	0.92
FAST score[†]	3 [2, 3]	3 [2, 3]	3 [2, 3]	0.63
Systolic BP (mmHg)	181 [148, 194]	156 [147, 190]	174 [152, 193]	0.74
At 2 hours				
SSS (/58)	55 [54, 56]	28 [15, 36]	40 [32, 51]	<0.001
Systolic BP (mmHg)	157 [148, 170]	154 [144, 177]	174 [146, 185]	0.52
At day 90				
mRS	1 [1, 2]	5 [3, 6]	3 [2, 5]	<0.01
Death (%)[‡]	0	8 (38.1)	2 (18.2)	0.10

mRS: modified Rankin Scale

[†] FAST score analysed using binary logistic regression as all participants had a score of 2 or 3.

[‡] Death analysed using Fisher' exact test due to small event rates.

Supplement Table 2. Time intervals (minutes) from stroke onset to hospital admission for trial and non-trial patients. Data are median [range]; comparison by Mann-Whitney U test.

	Trial patients		Non-trial Patients		Difference	
Characteristic	n	Median [Range]	n	Median [Range]	(95% CI)	2p
Stroke onset to paramedic review	38	46 [9, 581]	37	34 [11, 697]	0 (-20, 16)	1.00
Paramedic review to leaving scene	36	32 [4, 63]	33	26 [6, 66]	4 (-3, 9)	0.23
Leaving scene to hospital arrival	35	15 [5, 30]	36	19 [4, 43]	-3 (-7, 1)	0.17
Paramedic review to hospital arrival	36	50 [21, 76]	36	48 [9, 80]	1 (-6, 8)	0.70
Stroke onset to hospital arrival	37	84 [35, 650]	40	93 [42, 749]	-3 (-30, 16)	0.74
Stroke to randomisation	41	55 [7, 620]				
Randomisation to 15 minute assessment	40	15 [5, 30]				
Randomisation to 120 minute assessment	41	134 [100, 185]				

Supplement Table 3. Serious adverse events during the treatment period (7 days) by treatment group. Data are no. (%); comparison by Fisher exact test.

SAE	GTN	No GTN	2p
Complication of initial stroke	2 (8.0)	2 (12.5)	0.64
Extension of initial stroke	3 (12.0)	1 (6.3)	1.00
Recurrent or new stroke/TIA	2 (8.0)	4 (25.0)	0.19
Significant Carotid Stenosis	0 (0)	1 (6.3)	0.39
Bradycardia	1 (4.0)	0 (0)	1.00
Falls/Collapse	1 (4.0)	0 (0)	1.00
Malignancy	1 (4.0)	1 (6.3)	1.00
Pneumonia	3 (12.0)	2 (12.5)	1.00
Renal impairment	1 (4.0)	0 (0)	1.00
Seizure	0 (0)	1 (6.3)	0.39
Urinary Tract Infection	1 (4.0)	0 (0)	1.00

Extension of initial stroke was defined as a progression of neurological symptoms or signs in the same vascular territory within 72 hours of the qualifying stroke. Recurrent stroke/TIA was defined as stroke occurring greater than 72 hours after the qualifying stroke if the event was in the same vascular territory, or occurring at any time after the qualifying stroke if the event occured in a different vascular territory.

Supplement figure 1. Kaplan-Meirer curve for death over 90 days of follow-up. Comparison by Cox proportional regression with adjustment for age, p=0.15.