Baseline characteristics of the 1149 patients recruited into the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) randomised controlled trial

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Tables & figures

Declarations

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P Scutt: No declarations
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ABSTRACT

Background: High blood pressure (BP) is common in acute stroke and associated with a worse functional outcome. Glyceryl trinitrate (GTN), a nitric oxide donor, lowers BP in acute stroke and may improve outcome.

Aims: RIGHT-2 tested the feasibility of performing a UK multicentre ambulance-based stroke trial, and the safety and efficacy of GTN when administered by paramedics before hospital admission.

Methods: Paramedic-led ambulance-based multi-centre prospective randomised single-blind blinded-endpoint parallel-group controlled trial of transdermal GTN (given for 4 days) versus sham in patients with ultra-acute (<4 hours) presumed stroke. Data are number (%), median [interquartile range] or mean (standard deviation).

Results: Recruitment ran from October 2015 to 31st May 2018. 1,149 patients were recruited from 8 UK Ambulance Services and taken to 54 acute hospitals. Baseline characteristics include: mean age 73 (15) years; female 555 (48%); median time from stroke to randomisation 70 [45, 115] minutes; Face-Arm-Speech scale score 2.6 (0.5); and blood pressure 162 (25)/92 (18) mmHg. The final diagnosis was ischaemic stroke 52%, haemorrhagic stroke 13%, TIA 9%, and mimic 25%. The main trial results will be presented in quarter 4 2018. The results will also be included in updated Cochrane systematic reviews, and individual patient data meta-analyses of all relevant randomised controlled trials.

Conclusion: It was feasible to perform a multicentre ambulance-based ultra-acute stroke trial in the UK, and to treat with GTN versus sham. The relatively unselected cohort of stroke patients is broadly representative of those admitted to hospital in the UK.

Trial registration: ISRCTN26986053

INTRODUCTION

Nitric oxide (NO) donors are candidate treatments for acute ischaemic and haemorrhagic stroke.(1-3) NO is a cerebral and systemic vasodilator and so has the potential for: improving cerebral perfusion and lowering blood pressure; modulating vascular function through protecting endothelium and preventing smooth muscle cell proliferation; modifying neuronal function, in part through acting as a neurotransmitter; attenuating inflammation through reducing white cell function; and inhibiting apoptosis. In preclinical studies of cerebral ischaemia, NO donors reduced stroke lesion size, and improved regional cerebral blood flow (CBF) and functional outcome.(4, 5) Two NO donors have been tested in small clinical studies of patients with acute or recent stroke. Intravenous sodium nitroprusside (SNP) reduced BP, attenuated platelet function, but did not alter CBF;(6) the antiplatelet effects suggest that SNP should not be used in haemorrhagic stroke. In four pilot trials, transdermal glyceryl trinitrate (GTN, nitroglycerin) lowered BP by approximately 8% (with later effects attenuated by tachyphylaxis) and improved aortic vascular compliance; in contrast, it had no effects on platelet function, middle cerebral artery blood flow velocity or regional CBF.(7-10) Use of a transdermal preparation meant that the drug was simple to administer and could be given to patients with dysphagia.

As a result of these data, the large international Efficacy of Nitric Oxide in Stroke (ENOS) trial was performed in 4011 patients with acute stroke; GTN was safe to administer but did not alter functional outcome.(11) However, in a pre-defined subgroup, patients randomised within 6 hours of onset had improved functional outcome,(12) a result mirrored by those from the small Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT) where GTN was given within 4 hours of stroke onset (median onset-to-randomisation of 55 minutes) by paramedics prior to hospital admission.(10) In an individual patient data meta-analysis of all of these trials,(7-11) GTN was feasible to administer and safe.(13) Importantly, treatment improved multiple outcomes if given within 6 hours, these including significant reductions in dependency, disability, cognitive impairment, mood disturbance, and death, and improved quality of life.(13)

High systolic blood pressure (SBP >140 mmHg) is present in 70% or more of patients with acute stroke and is associated with a worse outcome (early recurrence, death

within a few weeks, combined death and dependency after several months.(14-17) Lowering BP might therefore reduce these events and improve functional outcome, provided that cerebral perfusion is not critically reduced.

Taking account of the potential importance of lowering BP in acute stroke, the antihypertensive properties of GTN, and potential benefit if given in the very early hours after stroke, the phase III Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) was run in the UK to test the safety and efficacy of GTN.(18, 19) The study involved recruitment, consent and initial treatment by paramedics at the scene with the aim of accelerating time to treatment. In a second objective, RIGHT-2 assessed the feasibility of performing large multicentre ambulance-based trials. Recruitment completed on 31st May 2018.

The aims of this paper are to present the baseline characteristics of included patients and summarise issues with delivery of the trial.

METHODS

Eligibility and consent

Details on the inclusion and exclusion criteria are given in the published protocol (18) and in the latest version of the protocol (Appendix A). Trial-trained paramedics considered all adult patients with suspected stroke they attended in the context of an emergency 999 telephone call. Patients had to have a face-arm-speech time (FAST) score of 2 or 3, be within 4 hours of symptom onset, and have systolic BP $\geq$120 mmHg. Patients with capacity (assessed using a short set of questions) gave written informed consent at the stroke scene prior to enrolment. Patients lacking capacity (e.g. due to drowsiness, dysphasia or confusion) had proxy consent given by a relative, if present, or a paramedic at the scene. No screening logs were kept by either participating paramedics or in ambulance.

Investigational medicinal product

The investigational medicinal product was transdermal GTN (5mg daily for four days, Transiderm Nitro "5" Novartis Pharmaceuticals Ltd, UK).(18) In the absence of matching placebo patches, patients randomised to the control group received a sham dressing of similar size and look to the GTN patch (DuoDERM – a hydrocolloid dressing, ConvaTec Ltd, UK). Patches and plasters came individually packed in sachets; four sachets were placed within a larger plastic box (treatment pack) that also contained a Patient Information Sheet, Consent Form and ambulance Case Report Form. Packs were prepared by the Nottingham University Hospitals NHS Trust Pharmacy.

Randomisation and data collection

Following consent, the paramedic opened the sealed treatment pack to enter a patient into the study. After completing the baseline ambulance case report form, the paramedic placed a patch/plaster on the patients back or shoulders.(18) Routine ambulance-based procedures were performed in parallel, after which the patient was then taken to hospital for further clinical management. The remaining three patches or plasters were given daily on days 2-4.

Outcomes

The primary and main secondary outcomes were collected centrally on day 90 by a

treatment-blinded assessor. Prior to this, they contacted the general practitioner to check that the patient was still alive, and then telephoned the patient (or carer as appropriate). Where telephone contact could not be made, outcome information was collected via a postal questionnaire. Final diagnosis was determined from the local investigator's diagnosis, ideally at discharge from hospital or before this at day 4 or on admission if discharge information was not available. The primary outcome was dependency assessed using the modified Rankin Scale (mRS) at day 90.(18) The mRS will be analysed across all 7 levels using ordinal logistic regression.(19) Secondary outcomes include early events at day 4; and measures of disability (Barthel Index), cognition (telephone-mini-mental state examination [t-MMSE], telephone interview for cognitive status-modified [TICS-M]), mood (Zung depression scale) and quality of life (Euro-QoL) at day 90; death. The effect of ambulance-administered GTN will be assessed on brain scanning following hospital admission in patients with ischaemic stroke (occluded artery, tissue hypoattenuation, lesion extent, swelling) and intracerebral haemorrhage (haematoma size, intraventricular haemorrhage, swelling); a research CT or MR scan on day 2 in some patients will allow progression of these measures to be assessed. Safety outcomes included all-cause and cause-specific case fatality; early neurological deterioration (based on change in NIHSS); hypotension (SBP<90 mmHg) or hypertension (SBP>180 mmHg) during treatment; and serious adverse events (all up to day 5, and fatal from day 5).(18)

Use of the internet

The RIGHT-2 trial used a secure internet site to collect data in real time on-line:

- Trial website: http://right-2.ac.uk
- Secure website for real time data entry and validation: https://www-apache.nottingham.ac.uk/~nszwww/right-2/live/right-2_login.php
- Demo website for investigators to practise data entry: https://www-apache.nottingham.ac.uk/~nszwww/right-2/demo/right-2_login.php
  (log-in: demoinv1; password: nottingham; pin: 8888)
- Secure website for upload of brain scans

Funding and governance

Planning for RIGHT-2 commenced in 2014 following the results of the RIGHT and ENOS trials of GTN.(10, 12) Funding for the trial was awarded by the British Heart Foundation in September 2014.

The trial was supervised by a Trial Steering Committee, run by a Trial Management Committee (based in Nottingham UK), and was monitored by an independent Data Monitoring Committee. By the end of recruitment, the DMC had met and assessed safety and efficacy on 6 planned occasions; on each occasion they recommended continuation of the trial. Independent experts adjudicated brain scans and serious adverse events, blinded to treatment. An International Advisory Committee assisted with advice on trial populations and the primary analysis.

RESULTS

Trial delivery

Throughout the trial, 5 protocol amendments were made covering multiple issues. Two key changes were made (in order of introduction):

1. Addition of a substudy exploring the experiences and perspectives of participating paramedics
2. Increase in sample size from 850 (18) to 1050 and then 1100 patients reflecting the presence of a higher than anticipated proportion of mimics (i.e. not stroke or TIA, originally expected to be ~12% but in reality reaching 25%)

Additionally, a change to the plan on analysis of the mRS was introduced, again because of the high mimic rate which would lead to a dilution of any treatment effect. Rather than performing a shift analysis in all patients (intention to treat, ITT), a hierarchical approach will be taken with the first analysis in the target population of patients with a final diagnosis of stroke or TIA (i.e. excluding mimics), this amounting to a modified ITT analysis. TIA is included since a positive treatment effect might be associated with a change in diagnosis from mild stroke to TIA. If this modified ITT analysis is statistically significantly positive, then the analysis will be performed in all patients as per ITT. The proposal to change the method of analysis of the primary outcome was presented to, and approved by, the Trial Steering Committee in April 2017, and subsequently by the International Advisory Committee; this decision was made without knowledge of unblinded data. The final Statistical Analysis Plan was submitted for publication in quarter 1 2018 prior to the planned unblinding of the data in quarter 3 2018.(19) This plan supersedes the original intention given in the published protocol.(18)

Baseline characteristics

The following data are given as number (%), median [interquartile range] or mean (standard deviation, SD). 1149 participants were recruited between 22nd October 2015 and 23rd May 2018 (Figure 1) from 8 ambulance services (AS, 7 in England plus Welsh AS) by 516 paramedics; these participants were taken to 54 hospitals.

The baseline clinical characteristics collected in the ambulance at the time of randomisation are presented in Table 1. Key features include: mean age 72.5 (14.6)

years; female 555 (48.3%); median time from onset to randomisation 70 [45, 115] hours (Figure 2); face-arm-speech-time test 2.6 (0.5); and mean blood pressure 162.1 (25.1)/ 91.6 (17.9) mmHg. Further information was collected in hospital (when treatment had already been administered) and this is shown in Appendix Table 1. This division between baseline characteristics in the ambulance and hospital admission characteristics is important because some hospital variables may have been influenced by GTN if it alters outcome, e.g. stroke severity, stroke syndrome (20) and final diagnosis of minor stroke versus TIA. At hospital, mean severity (National Institutes of Health Stroke Scale, NIHSS) 9.5 (7.5); Glasgow coma score 13.9 (1.7); and final diagnosis haemorrhagic stroke 144 (12.5%), ischaemic stroke 593 (52.0%), TIA 108 (9.4%), mimic 283 (24.6%). When comparing patient characteristics by final diagnosis, blood pressure was higher in haemorrhagic than ischaemic stroke (176/100 vs 161/90, $p<0.0001$). The mimic population (i.e. not stroke or TIA) included multiple diagnoses, commonly related to a seizure/fit, migraine/headache, or functional/psychosomatic disorder.

During the trial's progress, a number of logistical issues arose (Appendix Table 2) including the feasibility of ambulance services and hospitals joining the trial, consent in ambulance and re-consent in hospital, availability and losses of IMP, and a cyber-attack. Those related to consent and IMP management by paramedics will be addressed specifically in a subsequent publication.

Appendix Table 3 shows univariate relationships between key baseline or hospital admission factors, including year of randomisation into the trial. As the trial progressed, time from onset to randomisation, and proportion of mimics (versus other diagnoses) increased. Further, increasing time from onset to randomisation was associated with less severe stroke (lower NIHSS) and proportion of strokes; higher SBP was associated with increasing age, female sex and haemorrhagic stroke; and increasing age was associated with being female, stroke severity, higher SBP, and a longer time to randomisation.

DISCUSSION

It was feasible to perform a multicentre ambulance-based ultra-acute stroke trial in the UK, and to treat with GTN versus sham. The relatively unselected cohort of stroke patients is broadly representative of those admitted to hospital in the UK. Following completion of data validation, the database will be locked and the trial unblinded and analysed. It is intended to present the main results in quarter 4 2018, with the main manuscript published in parallel. Multiple pre-specified secondary publications and analyses are planned and some are listed in the statistical analysis plan.

RIGHT-2 data will be shared with prospective individual patient data meta-analyses, in particular the Blood pressure in Acute Stroke Collaboration (21) which encompasses an update of trials of GTN for stroke (13) and an ongoing analysis of trials of BP lowering in acute haemorrhagic stroke. Individual patient data will be shared with the Virtual International Stroke Trials Archive;(22) ultimately, a subset of data will be made available on the internet akin to the International Stroke Trial,(23) and anonymised neuroimaging data will be published.(24) Summary data will be added to updates of Cochrane Collaboration reviews.(25, 26)

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Table 1. Baseline ambulance characteristics of patients enrolled in the RIGHT-2 trial. Data are number (%), median [IQR], or mean (standard deviation)

	All	HS	IS	TIA	Mimic	p
Patients	1149	144	597	108	283	
Age (years)	72.5 (14.6)	73.2 (13.0)	75.1 (12.4)	73.2 (13.0)	66.3 (18.1)	<0.0001
Sex, male (%)	594 (51.7)	81 (56.3)	310 (51.9)	62 (57.4)	132 (46.6)	0.14
OTR (hours)	70 [45, 115]	74 [45, 110]	66 [45, 107]	79 [49, 106]	75 [47, 126]	0.066
<=1 hour (%)	491 (42.7)	59 (41.0)	279 (46.7)	40 (37.0)	106 (37.5)	0.033
ECG						
Sinus	659 (71.9)	92 (78.6)	320 (65.6)	61 (72.6)	178 (82.0)	0.0001
AF	187 (20.4)	15 (12.8)	128 (26.2)	15 (17.9)	26 (12.0)	-
Other	71 (7.7)	10 (8.5)	40 (8.2)	8 (9.5)	13 (6.0)	-
Systolic BP (mmHg)	162.1 (25.1)	176.0 (27.0)	160.6 (23.3)	161.3 (24.0)	159.1 (26.4)	<0.0001
Diastolic BP (mmHg)	91.6 (17.9)	100.1 (21.6)	90.0 (17.4)	91.6 (16.3)	90.7 (16.3)	<0.0001
Heart rate (bpm)	82.2 (18.6)	81.5 (16.6)	82.7 (19.7)	78.3 (14.7)	83.4 (18.6)	0.091
Oxygen saturation (%)	96.3 (2.8)	95.7 (3.1)	96.3 (2.8)	96.4 (2.3)	96.5 (2.8)	0.040
Temperature (°C)	36.5 (0.6)	36.4 (0.6)	36.5 (0.6)	36.6 (0.6)	36.7 (0.7)	<0.0001
Glucose (mmol/L)	7.6 (3.4)	7.5 (3.3)	7.7 (3.5)	7 (2.6)	7.5 (3.4)	0.22
GCS [/15]	13.9 (1.7)	13.6 (1.8)	13.8 (1.7)	14.7 (0.8)	13.9 (1.8)	<0.0001
<14 (%)	302 (26.4)	49 (34.0)	173 (29.0)	6 (5.6)	69 (24.6)	<0.0001
FAST score [/3]	2.6 (0.5)	2.8 (0.4)	2.6 (0.5)	2.4 (0.5)	2.5 (0.5)	<0.0001
=3 (%)	690 (60.2)	110 (76.4)	391 (65.5)	42 (38.9)	137 (48.6)	<0.0001
Source of consent (%)						
Patient	603 (52.5)	60 (41.7)	281 (47.1)	84 (77.8)	169 (59.7)	<0.0001
Relative	406 (35.4)	63 (43.8)	242 (40.5)	17 (15.7)	79 (27.9)	-
Close friend	23 (2)	6 (4.2)	9 (1.5)	4 (3.7)	4 (1.4)	-
Paramedic	116 (10.1)	15 (10.4)	65 (10.9)	3 (2.8)	31 (11.0)	-
Enrolling AS (%)						
East Midlands	218 (19)	25 (17.4)	121 (20.3)	21 (19.4)	46 (16.3)	0.12
East of England	178 (15.5)	23 (16.0)	89 (14.9)	13 (12.0)	53 (18.7)	-
London	202 (17.6)	19 (13.2)	90 (15.1)	21 (19.4)	70 (24.7)	-
South Central	7 (0.6)	1 (0.7)	5 (0.8)	0 (0)	1 (0.4)	-
South-West	265 (23.1)	39 (27.1)	142 (23.8)	28 (25.9)	53 (18.7)	-
Welsh	89 (7.7)	9 (6.3)	49 (8.2)	12 (11.1)	17 (6.0)	-
West Midlands	37 (3.2)	4 (2.8)	20 (3.4)	2 (1.9)	10 (3.5)	-
Yorkshire	153 (13.3)	24 (16.7)	81 (13.6)	11 (10.2)	33 (11.7)	-

AS: Ambulance Service; BP: blood pressure; GCS: Glasgow coma scale; OTR: onset to randomisation

Figure 1. Recruitment throughout the trial.

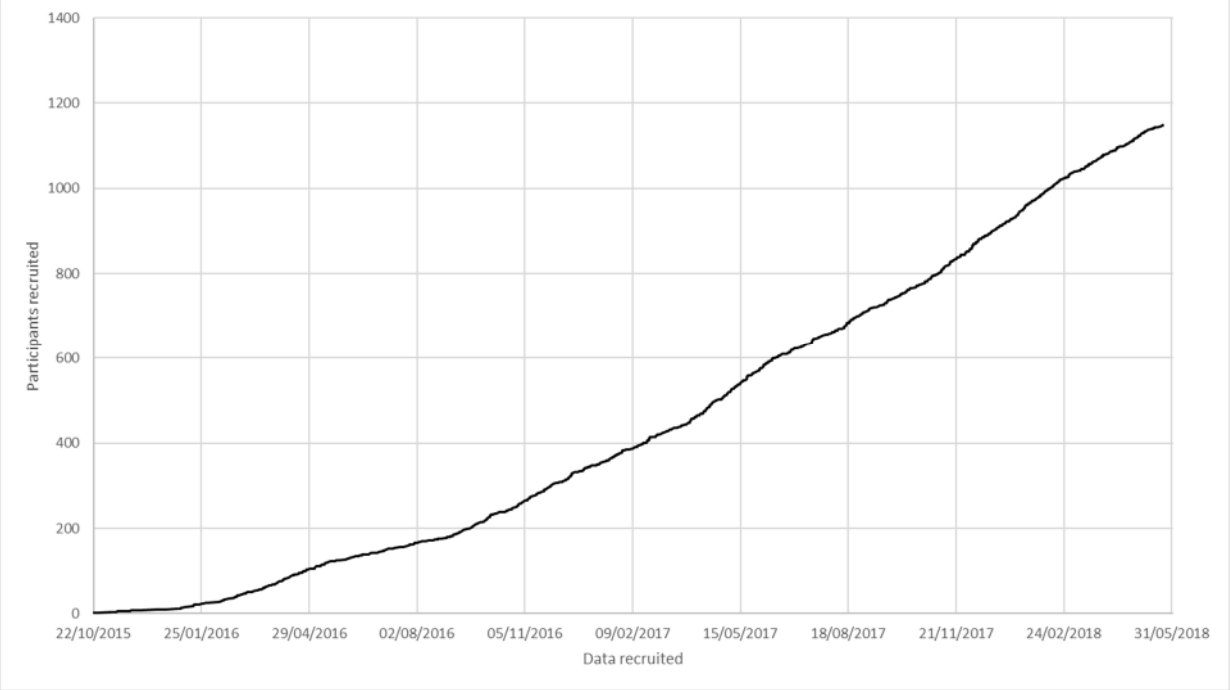
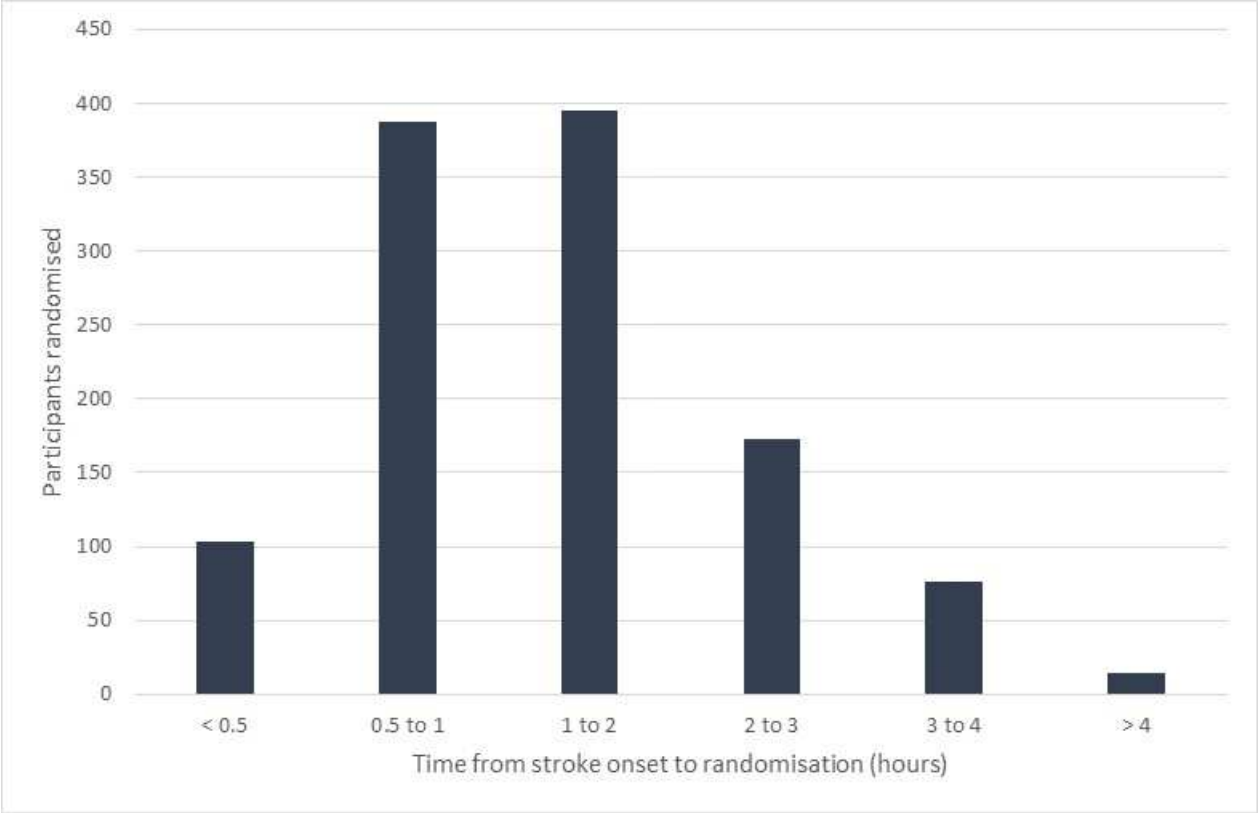


Figure 2. Histogram of time from onset to randomisation



ON-LINE APPENDIX

Baseline characteristics of the 1149 patients recruited into the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2)

Philip M Bath, Polly Scutt, Jason P Appleton, Mark Dixon, Lisa J Woodhouse, Joanna M Wardlaw, Nikola Sprigg

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Appendix Table 1. Recorded patient characteristics at hospital admission. Data are number (%), median [IQR], or mean (standard deviation)

	All	HS	IS	TIA	Mimic	p
Number of patients	1149	144	597	108	283	
Ethnic group (%)						
White	1014 (90)	128 (88.9)	543 (91.0)	98 (92.5)	244 (87.5)	0.27
Black	47 (4.2)	6 (4.2)	24 (4)	3 (2.8)	14 (5.0)	-
Asian, east	42 (3.7)	5 (3.5)	19 (3.2)	4 (3.8)	14 (5.0)	-
Asian, south-east	3 (0.3)	0 (0)	1 (0.2)	0 (0)	2 (0.7)	-
Asian, south	2 (0.2)	2 (1.4)	0 (0)	0 (0)	0 (0)	-
Asian, other	8 (0.7)	1 (0.7)	4 (0.7)	1 (0.9)	2 (0.7)	-
Other	11 (1.0)	2 (1.4)	6 (1.0)	0 (0)	3 (1.1)	-
Disposition (before stroke onset) (%)						
Home – independent	854 (75.6)	123 (86.6)	457 (76.5)	87 (81.3)	187 (66.1)	0.0005
Warden-aided flat	21 (1.9)	1 (0.7)	14 (2.3)	1 (0.9)	5 (1.8)	-
Home – needing care	164 (14.5)	11 (7.7)	80 (13.4)	8 (7.5)	65 (23.0)	-
Carer's home	14 (1.2)	0 (0)	10 (1.7)	1 (0.9)	3 (1.1)	-
Respite care	4 (0.4)	0 (0)	2 (0.3)	0 (0)	2 (0.7)	-
Residential home	30 (2.7)	4 (2.8)	14 (2.3)	6 (5.6)	6 (2.1)	-
Care home	12 (1.1)	2 (1.4)	6 (1.0)	3 (2.8)	1 (0.4)	-
Nursing home	8 (0.7)	0 (0)	5 (0.8)	1 (0.9)	2 (0.7)	-
Rehabilitation hospital	3 (0.3)	0 (0)	2 (0.3)	0 (0)	1 (0.4)	-
Other	20 (1.8)	1 (0.7)	7 (1.2)	0 (0)	11 (3.9)	-
Pre-morbid mRS [/6]	0 [0, 2]	0 [0, 1]	0 [0, 2]	0 [0, 2]	1 [0, 3]	0.0005
>2 (%)	223 (19.7)	17 (11.8)	107 (17.9)	19 (17.6)	79 (27.9)	0.0002
Pre-morbid EuroQol–5D *	0.7 (0.3)	0.6 (0.4)	0.8 (0.3)	0.8 (0.3)	0.7 (0.3)	<0.0001
Medical history (%)						
Hypertension	643 (57.1)	82 (57.3)	355 (59.5)	64 (59.8)	142 (51.1)	0.12
Diabetes mellitus	227 (20.1)	22 (15.4)	125 (20.9)	19 (17.8)	61 (21.9)	0.37
Atrial fibrillation	234 (20.8)	23 (16.1)	147 (24.6)	17 (15.9)	47 (16.8)	0.010
Previous stroke	272 (24.2)	27 (18.9)	137 (22.9)	22 (20.6)	85 (30.6)	0.022
Previous TIA	177 (15.8)	14 (9.9)	76 (12.8)	30 (28.3)	56 (20.3)	<0.0001
Ischaemic heart disease	196 (17.5)	16 (11.3)	103 (17.3)	19 (17.8)	58 (21.1)	0.10
Peripheral arterial disease	19 (1.7)	2 (1.4)	10 (1.7)	3 (2.8)	4 (1.5)	0.81
Family history of young stroke	12 (1.3)	0 (0)	10 (2.0)	0 (0)	2 (0.9)	0.18
BP lowering medication	560 (50.3)	62 (44.6)	317 (53.5)	57 (53.3)	124 (45.1)	0.054
Lipid lowering medication	444 (39.9)	49 (35.3)	226 (38.2)	48 (44.9)	121 (44.0)	0.18
Nitrate therapy	58 (5.2)	3 (2.2)	32 (5.4)	6 (5.6)	17 (6.2)	0.36
Smoking, current	168 (18.2)	9 (9.1)	91 (17.8)	14 (16.3)	54 (23.7)	0.043
Alcohol intake, >21 upw	57 (6.6)	7 (7.1)	38 (7.9)	4 (5.2)	8 (3.8)	0.037
Qualifying event (%)						
Intracerebral haemorrhage	144 (12.5)	144 (100)	0 (0)	0 (0)	0 (0)	-
Ischaemic stroke	597 (52.0)	0 (0)	597 (100)	0 (0)	0 (0)	-
Stroke type unknown	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)	-
TIA	108 (9.4)	0 (0)	0 (0)	108 (100)	0 (0)	-

Non-stroke / mimic	283 (24.6)	0 (0)	0 (0)	0 (0)	283 (100)	-
OCSP syndrome (%) (20)						
Total anterior circulation	351 (33.5)	77 (55.0)	222 (37.9)	10 (10.8)	42 (18.4)	<0.0001
Partial anterior circulation	416 (39.7)	42 (30.0)	232 (39.6)	40 (43.0)	102 (44.7)	-
Lacunar	243 (23.2)	18 (12.9)	114 (19.5)	39 (41.9)	72 (31.6)	
Posterior circulation	37 (3.5)	3 (2.1)	18 (3.1)	4 (4.3)	12 (5.3)	
IV thrombolysis (%)	295 (26)	0 (0)	283 (47.4)	1 (0.9)	11 (3.9)	<0.0001
Feeding status (%)						
Normal diet	625 (56.5)	30 (21.3)	273 (46.2)	98 (94.2)	224 (83.3)	<0.0001
Soft diet	103 (9.3)	9 (6.4)	76 (12.9)	1 (1)	16 (5.9)	
Nasogastric feed only	48 (4.3)	14 (9.9)	27 (4.6)	1 (1)	6 (2.2)	
PEG feed only	4 (0.4)	1 (0.7)	2 (0.3)	0 (0)	1 (0.4)	
Intravenous/subcutaneous fluids only	148 (13.4)	35 (24.8)	106 (17.9)	0 (0)	7 (2.6)	
Nothing	178 (16.1)	52 (36.9)	107 (18.1)	4 (3.8)	15 (5.6)	
Systolic blood pressure (mmHg)	155.5 (25.8)	169.1 (27.2)	154.7 (23.6)	151.4 (26.4)	151.7 (27.1)	<0.0001
Diastolic blood pressure (mmHg)	83.7 (16.2)	90.6 (18.8)	82.6 (15.6)	83.1 (15.5)	82.8 (15.4)	<0.0001
Heart rate (bpm)	79.4 (17.9)	77.9 (16.4)	80.4 (18.9)	77.9 (16.9)	78.5 (16.4)	0.25
Glucose (mmol/L)	7.5 (3.3)	7.5 (3.3)	7.7 (3.2)	6.8 (2.7)	7.3 (3.6)	0.074
Temperature (°C)	36.4 (0.6)	36.3 (0.7)	36.4 (0.5)	36.4 (0.5)	36.5 (0.6)	0.0010
Weight (kg)	74.1 (17.4)	72.7 (15.2)	74.7 (18.2)	76.2 (17.1)	72.5 (16.3)	0.24
Glasgow coma scale [/15]	13.8 (2.1)	12.3 (3.3)	13.8 (1.8)	14.8 (0.5)	14.3 (1.6)	<0.0001
NIHSS (/42)	9.5 (7.5)	15.4 (7.2)	10.6 (7.2)	2.9 (3.3)	5.6 (5.8)	<0.0001
BP lowering drugs (%)						
ACE-I	248 (21.6)	23 (16.0)	140 (23.5)	25 (23.1)	60 (21.2)	0.26
Angiotensin receptor antagonist	105 (9.1)	13 (9.0)	57 (9.5)	10 (9.3)	25 (8.8)	0.99
ß-receptor antagonist	266 (23.2)	23 (16.0)	166 (27.8)	25 (23.1)	52 (18.4)	0.0020
Calcium channel blocker	215 (18.7)	23 (16.0)	128 (21.4)	12 (11.1)	52 (18.4)	0.055
Diuretic	83 (7.2)	7 (4.9)	46 (7.7)	7 (6.5)	23 (8.1)	0.62
α-receptor antagonist	41 (3.6)	3 (2.1)	24 (4.0)	4 (3.7)	10 (3.5)	0.74
Centrally acting	3 (0.3)	1 (0.7)	2 (0.3)	0 (0)	0 (0)	0.54
Other	30 (2.6)	3 (2.1)	14 (2.3)	4 (3.7)	9 (3.2)	0.76
Number taken, median	1 [0, 2]	0 [0, 1]	1 [0, 2]	1 [0, 1]	0 [0, 2]	-
0 (%)	537 (47.8)	75 (52.4)	261 (43.9)	50 (46.7)	150 (54.0)	0.092
1 (%)	284 (25.3)	44 (30.8)	154 (25.9)	31 (29.0)	55 (19.8)	
2 (%)	210 (18.7)	18 (12.6)	124 (20.8)	21 (19.6)	47 (16.9)	
3 (%)	66 (5.9)	4 (2.8)	38 (6.4)	4 (3.7)	20 (7.2)	
4+ (%)	27 (2.4)	2 (1.4)	18 (3.0)	1 (0.9)	6 (2.2)	
CT/MRI scan, hospital report †						
Normal/no presenting lesion seen	571 (52.6)	0 (0)	292 (49.6)	86 (84.3)	193 (77.2)	<0.0001
IS, no HTI	264 (24.3)	0 (0)	259 (44.0)	2 (2)	3 (1.2)	
IS, with HTI	8 (0.7)	0 (0)	7 (1.2)	0 (0)	1 (0.4)	

HS	141 (13)	139 (97.2)	0 (0)	0 (0)	2 (0.8)	
Other	101 (9.3)	4 (2.8)	31 (5.3)	14 (13.7)	51 (20.4)	
Imaging compatible with clinical presentation	791 (80.5)	141 (99.3)	451 (84.1)	65 (67.0)	134 (65.0)	<0.0001
Mass effect	115 (10.7)	81 (57.9)	23 (3.9)	1 (1.0)	10 (4.1)	<0.0001
Cerebral atrophy	250 (23.4)	27 (19.7)	160 (27.3)	21 (20.4)	41 (17.1)	0.0077
Periventricular lucency	211 (19.7)	26 (19.0)	126 (21.4)	21 (20.6)	38 (15.8)	0.31
Previous stroke	273 (25.3)	28 (20.0)	144 (24.5)	27 (26.2)	73 (29.4)	0.21

BP: blood pressure; CT: computerised tomography; HS: haemorrhagic stroke; HTI: haemorrhagic transformation; IS: ischaemic stroke; MRI: magnetic resonance imaging; TIA: transient ischaemic attack
† Unadjudicated

Appendix Table 2. Issues with delivery of the trial.

Issue	Explanation	Effect/response
Hospital feasibility	A) Potential conflict with in-hospital hyperacute studies or commercial studies. B) Reduced operational hours due to imaging capacity C) Delays in site setup.	A) Hospitals imposed recruitment time restrictions (0800-1700 M-F / 2200-0600) or withdrew part-way through the set-up/recruitment phase to minimise loss of recruitment to other hyperacute stroke research studies B) Out of hours imaging for non-urgent cases not feasible, therefore trial operational hours reduced to allow research imaging to be completed C) A few hospitals did not complete setup phase despite interest from ambulance services. Some paramedics had already completed the trial training in these areas in preparation
Ambulance service feasibility	Limited capacity to deliver the trial despite interest received from hyperacute stroke centres	Limited capacity in some ambulance services or concurrent studies led to non-participation or participation in smaller localities.
Variation in ambulance service operational delivery	Each ambulance trust operates individually requiring specific adjustments to ensure the trial protocol was deliverable	Adjustments to data collection and local accountability processes ensured feasibility of trial delivery per ambulance service
Concurrent hyperacute research	Delayed opening of hospital sites due to concurrent cluster randomised controlled trial	Co-enrolment discussed and agreed, some hospital sites opted to wait until concurrent trial has concluded
Half-point research accruals	Research accrual point split between recruiting ambulance service and hospital	Due to two organisations involved in the recruitment and continuation of care, the recruitment accrual point was awarded between hospital and ambulance service on

		an alternating basis. Many institutions found this unsatisfactory
Prolonged IMP manufacture	Internal department inspections delayed production and Quality Person check process prior to IMP release	Delay in release of treatment packs to some ambulance services thereby delaying recruitment
Insufficient paramedics	Work pressure, operational demands	Addition of more ambulance stations and hospitals within existing ambulance Services. Addition of more ambulance services. Explored participation of emergency medical technicians; although probably feasible, this was not pursued
Use of private ambulance providers	Private ambulance companies occasionally utilised to support with frontline demand	Feasible, but did not progress to participation
Notification of recruitment	Paramedic procedure to inform trial coordination centre of participant recruitment by telephone	Notification of recruitment not always received from recruiting paramedic due to operational pressures. Some participants not located at hospital due to unawareness of enrolment
Participant conveyed to non-participating hospital	Not every hyperacute stroke unit within an ambulance service area participated in RIGHT-2 due to capacity and feasibility. A few recruited patients were taken to hospitals that were yet to start-up	No treatment on days 2-4; no in-hospital data available (but still available for follow-up at days 90 and 365)
Recruitment of same patient twice	Patient attended by different paramedics at subsequent emergency call	Single incidence; patient discontinued treatment and follow-up
Apparent lack of consent in ambulance when presenting to hospital	Time pressure and severe stroke severity	File notes confirmed consent obtained; MHRA informed.
Mislaid IMP boxes	Alternative procedures	Temporary suspension of recruitment in one ambulance service; majority of missing IMP

		found. MHRA informed. Accountability procedure reviewed. Introduction of QR codes on IMP to facilitate tracking of IMP using smart-phones
Some hospitals do not allow research coordinators to take consent	CTIMP studies in some locations require consultant continued consent where proxy assent has been gained by paramedics	Participants unable to give informed consent in the ambulance due to lack of capacity; relative, carer, friend or paramedic proxy consent given at scene
Missed patches	Patches on days 2, 3 and 4 omitted at weekends	Research staff often work within office hours, contributing to delay in screening, continued consent and often missed patches when patients were recruited outside of working hours, and especially on Bank Holidays
Holiday research cover	Recruitment stopped and restarted over holiday periods	Due to reduced research team cover a few hospitals requested temporarily stopping recruitment over Easter/Christmas/Bank Holiday weekends. This led to confusion among paramedics as to when they could recruit
Hospital recruitment stop	Four hospitals stopped receiving patients prior to the end of RIGHT-2 recruitment	Reduction in recruitment across local areas, leading to a few patients being recruited to closed hospitals in error
Participant transfers to non-participating centre	Some neurointervention centres not participating in RIGHT-2.	Patients unable to continue with randomised treatment following transfer to non-participating centre.
Cyber attack	Cyber-attack of network hosting trial database and website	Database unavailable for < 1 week; automatic notifications not received by hospital staff leading to a failure of alerts for two cases
Return of unused IMP at closedown	<1% (14 out of 2800) treatment packs not located by ambulance services at trial closedown	A few IMP treatment packs were not located at the ambulance station to which they were originally assigned following recall after trial closure. Ambulance service teams (including make-ready departments as vehicles are rotated) continue to search and remain vigilant for the missing packs

IMP: investigational medicinal product; MHRA: Medicines and Healthcare products Regulatory Agency

Appendix Table 3. Univariate correlations between baseline characteristics. Correlations by point biserial or Spearman's tests; data are correlation coefficient and p value.

	Male	NIHSS	Event	SBP	OTR	Randomisation year
Age	**-0.12, <0.001**	**0.17, <0.001**	**0.19, <0.001**	**0.087, 0.003**	**0.073, 0.013**	0.050, 0.089
Male	X	-0.048, 0.14	0.058, 0.053	**-0.085, 0.004**	-0.036, 0.220	0.018, 0.55
NIHSS		X	0**.28, <0.001**	0.021, 0.529	-0.053, 0.108	0.003, 0.919
Event			X	**0.080, 0.007**	**-0.071, 0.017**	**-0.056, 0.058**
SBP				X	-0.006, 0.840	0.015, 0.61
OTR					X	**0.11, <0.001**

Event: haemorrhage stroke, ischaemic stroke, TIA, mimic; NIHSS: National Institutes of Health Stroke Scale (severity); OTR: onset to randomisation; SBP: systolic blood pressure