Pre-hospital transdermal glyceryl trinitrate in patients with stroke mimics: data from the RIGHT-2 randomised-controlled ambulance trial.

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ABSTRACT

Background: Prehospital stroke trials will inevitably recruit patients with non-stroke conditions, so called stroke mimics. We undertook a pre-specified analysis to determine outcomes in patients with mimics in the second Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT-2).

Methods: RIGHT-2 was a prospective, multicentre, paramedic-delivered, ambulance-based, sham-controlled, participant-and outcome-blinded, randomised-controlled trial of transdermal glyceryl trinitrate (GTN) in adults with ultra-acute presumed stroke in the UK. Final diagnosis (intracerebral haemorrhage, ischaemic stroke, transient ischaemic attack, mimic) was determined by the hospital investigator. This pre-specified subgroup analysis assessed the safety and efficacy of transdermal GTN (5 mg daily for 4 days) versus sham patch among stroke mimic patients. The primary outcome was the 7-level modified Rankin Scale (mRS) at 90 days.

Results

Among 1149 participants in RIGHT-2, 297 (26%) had a final diagnosis of mimic (GTN 134, sham 163). The mimic group were younger, mean age 67 (SD: 18) vs 75 (SD: 13) years, had a longer interval from symptom onset to randomisation, median 75 [95% CI: 47,126] vs 70 [95% CI:45,108] minutes, less atrial fibrillation and a lower systolic blood pressure and Face-Arm-Speech-Time tool score than the stroke group. The three most common mimic diagnoses were seizure (17%), migraine or primary headache disorder (17%) and functional disorders (14%). At 90 days, the GTN group had a better mRS score as compared to the sham group (adjusted common odds ratio 0.54; 95% confidence intervals 0.34, 0.85; p = 0.008), a difference that persisted at 365 days. There was no difference in the proportion of patients

who died in hospital, were discharged to a residential care facility, or suffered a serious adverse event.

Conclusions

One-quarter of patients suspected by paramedics to have an ultra-acute stroke were subsequently diagnosed with a non-stroke condition. GTN was associated with unexplained improved functional outcome observed at 90 days and one year, a finding that may represent an undetected baseline imbalance, chance, or real efficacy. GTN was not associated with harm.

Trial registration: This trial is registered with International Standard Randomised Controlled Trials Number ISRCTN 26986053.

Funding:

The RIGHT-2 trial was supported by the British Heart Foundation

Keywords: Stroke; mimic; functional stroke; migraine; seizures; glyceryl trinitrate; nitroglycerin; ambulance; paramedic

BACKGROUND

Glyceryl trinitrate (GTN) has several effects that may be beneficial in acute stroke. High blood pressure (BP) is common in the acute phase of stroke and associated with poor outcome (1). In-hospital BP lowering is recommended for patients with intracerebral haemorrhage (2), and the application of a glyceryl trinitrate (GTN) skin patch is a simple and efficient approach. GTN has other effects which may be beneficial in stroke such as topping up nitrate-depleted endothelium.

Stroke can be difficult to diagnose in the prehospital setting as there is no perfect or readily available diagnostic test. Conditions such as seizures, migraine and functional disorders can present with symptoms suggestive of a stroke, hence use of the term 'stroke mimics' (3). Mimics are estimated to account for 31% of presentations at hospital with suspected stroke (4). An incorrect working diagnosis of stroke may delay appropriate treatment for patients and expose them to unnecessary risk as some may receive stroke treatments such as thrombolysis before the correct diagnosis is confirmed. Equally, patients with a stroke may be deprived of life-changing treatment if their initial diagnosis is thought to be a mimic. Numerous factors have been reported to be associated with a greater probability of an event being a mimic rather than stroke, including younger age, female sex, fewer vascular risk factors, history of seizures and less severe presenting symptoms including a lower likelihood of facial or limb weakness, speech difficulty or acute hypertension (5, 6). The Face-Arms-Speech-Time (FAST) tool is widely used by ambulance paramedics to diagnose suspected stroke, and has a sensitivity of 79% (7). However, as it is limited to examining the patient for facial palsy, altered motor functioning of the arm and abnormal speech, FAST is less likely to identify mild or severe strokes and those affecting only the posterior circulation (8, 9)

The second Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) investigated the effects of ultra-acute administration of transdermal GTN versus sham patch by paramedics in 1149 patients with suspected stroke in the UK (10). Among the 297 (26%) participants with a final hospital diagnosis of a non-stroke condition, modified Rankin Scale (mRS) scores were better in those randomised to GTN compared to sham (10).The aim of this pre-specified subgroup analysis was to characterise stroke mimic cases

in a FAST positive population and to examine in detail the RIGHT-2 findings among participants with a stroke mimic as their final diagnosis.

METHODS

Study design and population

RIGHT-2 was a multicentre, prospective, randomised, sham-controlled, participant-and outcome-blinded, randomised-controlled trial in adults with ultra-acute presumed stroke in the UK. Paramedics from eight UK ambulance services (East Midlands, East of England, London, South Central, South West, Wales, West Midlands and Yorkshire) delivered the trial within the pre-hospital ambulance environment (10, 11). Briefly, adult patients were eligible for inclusion if they accessed care through an emergency ambulance telephone call for presumed stroke and were assessed within 4 hours of onset of their symptoms by a trial-trained paramedic from a participating ambulance service and could be transported to a participating hospital. Patients had to have at least two positive signs in the FAST test assessment (the number of positive signs was scored as a value out of a maximum of 3) and a systolic blood pressure (SBP) $\geq$120 mmHg. Patients from a nursing home, or with reduced consciousness (Glasgow coma scale [GCS] <8/15), hypoglycaemia (capillary glucose <2.5 mmol/l) or a witnessed seizure, were excluded. A sample size calculation determined that a total sample size of 850 participants (425 in each group) was required to detect a shift in mRS with a common odds ratio [OR] of 0·70 assuming an overall significance level of 5%, 90% power, 3% loss to follow-up, mimic and transient ischaemic attack rate of 20%, and reduction for baseline covariate adjustment of 20%. However, during the trial, the non-stroke diagnosis rate exceeded 30% and so the overall sample size was increased to 1050 to maintain the overall effect size and statistical power (10). Detailed inclusion and exclusion criteria and

additional information on the methods are given in the published protocol paper and in the Supplement to the main trial publication (11, 12).

The final diagnosis was made by the principal investigator based on clinical and neuroimaging findings, and categorised as intracerebral haemorrhage, ischaemic stroke, transient ischaemic attack (TIA) or stroke/TIA mimic. Brain scans were reviewed centrally by an expert panel of neuroradiologists who were aware of the time to scan and the side of symptoms but blinded to all other information to confirm diagnosis of ischaemic, haemorrhagic stroke or mimic with structural lesion. Diagnostic adjudication was completed without knowledge of the primary outcome. Patients who had a stroke mimic received the same follow-up at Day 365 as confirmed stroke and TIA cases.

Treatment

Participants were randomly assigned to receive transdermal GTN (nitroglycerin; 5 mg as Transiderm-Nitro® 5, Novartis, Frimley UK) or a similarly-appearing sham treatment not known to exert any pharmacological effect (DuoDERM® hydrocolloid dressing, Convatec, Flintshire UK) in a 1:1 ratio. Randomisation was stratified by ambulance station with blocks of four packs (two active, two control) in a random permuted order that was generated by the trial programmer at the Nottingham Stroke Trials Unit. Ambulances carried only one pack at a time and paramedics signed-out the treatment pack with the lowest randomisation number from their ambulance station at the start of their shift and returned it if unused at the end of their shift (10). The first treatment (GTN or sham) was administered by the paramedic immediately after randomisation in the ambulance; further treatments were given daily for up to three days in hospital but were stopped earlier if a non-stroke diagnosis was made. Each treatment pack was sealed to maintain blinding of paramedics. Participants were effectively

masked since the patches and dressings themselves were unlabelled, and a gauze dressing was taped over the top of the patch or dressing to provide additional masking.

Outcomes

The primary outcome was functional status assessed across the 7-levels of the mRS (0 = no dependency to 6 = death) (13) , measured at 90 days after randomisation. A trained assessor, masked to treatment allocation and using a structured questionnaire, obtained outcomes during a telephone interview with the participant. In cases where the participant was incapable of providing this information, the relative or carer was interviewed. If telephone contact could not be made after multiple attempts, a questionnaire was sent by post.

Participants were seen at Day 4 (or at hospital discharge, if earlier) to determine adherence to treatment and assess neurological deterioration. Duration of stay and discharge destination (to another hospital, institution or home) were also recorded. Pre-specified secondary clinical outcomes at Day 90 included activities of daily living (Barthel index, BI); cognition (modified telephone mini-mental state examination [MMSE]; telephone interview for cognition scale-modified [TICS-M]; and categorical verbal fluency using animal naming); health-related quality of life on the European quality of life-5 dimensions-3 level (EQ-5D-3L), from which a health status utility value (HSUV) was calculated with an EQ-visual analogue scale; and mood (abbreviated Zung depression score [ZDS]), all as used in the preceding Efficacy of Nitric Oxide in Stroke (ENOS) trial of GTN in hospital (10, 14). Home-time was calculated as the number of days between discharge and Day 90. As a secondary assessment time, clinical outcomes were re-obtained by telephone at one year.

Statistical analysis

Analyses followed the RIGHT-2 statistical analysis plan (15). The primary outcome (shift on 7-level mRS) was analysed using ordinal logistic regression with adjustment for age, sex, premorbid mRS, baseline FAST score and SBP, and time from the onset of symptoms to randomisation. The assumption of proportional odds was tested using the likelihood ratio test. We also performed unadjusted, per-protocol and imputed (missing mRS data estimated using multiple regression-based imputation) sensitivity analyses for completeness. Heterogeneity of the treatment effect on the primary outcome was assessed for the purpose of hypothesis-generation in pre-specified subgroups by adding an interaction term to an adjusted ordinal logistic regression model. Death was analysed using adjusted Cox proportional hazards regression models. Other outcomes were assessed using adjusted binary logistic regression, Cox regression, ordinal logistic regression, multiple linear regression and analysis of covariance (BP). A pre-specified global outcome (comprising ordered categorical or continuous data for mRS, BI, ZDS, TICS-M and EQ-5D-HSUV) was analysed using the Wei-Lachin test (16). Data are shown as number (%), median [interquartile range, IQR], mean (standard deviation, SD), difference in mean and odds ratio, with 95% confidence intervals (CI).

RESULTS

Demographics

From October 2015 to May 2018, 516 trial-trained paramedics enrolled 1149 participants into RIGHT-2 with follow-up continuing to 365 days. Among these 1149 patients, 297 (26%) were subsequently diagnosed with a stroke mimic (Figure 1). Compared to stroke cases and prior to randomisation, the mimic group were on average significantly younger, had a longer interval from symptom onset to randomisation, a lower proportion of atrial fibrillation/flutter, lower SBP, and fewer positive signs in their FAST assessment (Additional Table A).

Among the 297 patients with a stroke mimic, the mean age was 67 years (SD 18), 53% of participants were female, and 13% were non-white **(**Table 1). The GCS score was less than 14 in one quarter of mimic cases, and less than half were positive on all three FAST indicators (face/arm/speech). In the mimic group, the most common pre-existing medical conditions were hypertension (51%), previous stroke (31%), diabetes mellitus (21%) and heart disease (21%). Twenty-eight percent of participants in the study had a pre-existing dependence of a moderate or greater severity (mRS >2). The median time from symptom onset to randomisation was 75 minutes [IQR 47, 126].

Within the mimic group, 134 (45%) participants had been randomised to GTN and 163 (55%) to sham. Demographic and baseline clinical characteristics were similar between the GTN and sham groups except that the mean SBP was lower by 7.0 mmHg [95% CI -12.9–-1.1; p = 0.021] in the group randomised to GTN.

Mimic diagnoses

The three most common mimic diagnoses of epileptic seizure (17%), migraine or primary headache disorder (17%) and functional neurological disorder (14%), together accounted for 47% of the mimic group (Additional Table B). Other neurological (16%) and cardiovascular (7%) events represented a further 25% of presentations. A final diagnosis was unavailable in 9% of mimic cases with discharge records reporting exclusion of a stroke or TIA event but no clear diagnosis. The remaining 29% of mimic events represented a wide range of diagnoses. There was no significant difference in the proportions of final diagnoses between the treatment and sham group. In addition, for 36 participants, their qualifying event was diagnosed as an infection during at least one follow-up (Additional Table C).

Randomised treatment

Data on adherence to the trial protocol are available for 281 (95%) cases (Additional Table D). Adherence to the first randomised treatment was near complete in both GTN and sham groups (99.3% vs 100%) but overall, only 20% of participants with a stroke mimic received the first two patches. This decreased to 9% for application of all four patches. Adherence for treatment over 2 and 4 days were much lower than for stroke/TIA participants (12). The most common reason for non-adherence in the stroke mimic group was discontinuation following an early diagnosis of non-stroke (66%). There was no difference in adherence to protocol between the GTN and sham groups. However, patients with a final diagnosis of mimic received less treatment than those with a stroke diagnosis (Additional Table E).

There were 25 protocol violations in the ambulance; these were related to the inclusion of patients beyond 4 hours, low FAST score (<2), low SBP (<120 mmHg), resident in a nursing home, and failure to notify the hospital (Additional Table F). There were three protocol violations in hospital; two involved not administering the treatment on Day 2 and one was failure to obtain secondary consent.

Primary clinical outcome

The primary outcome (mRS score) was measured at 90 days in 274 (92%) participants in the mimic group. A minority of participants refused or were lost to follow-up. Participants randomised to sham treatment had a median mRS of 3 [1, 4] at 90 days (Table 2). Among participants with a mimic, GTN was associated with reduced likelihood of poor 90-day mRS score, compared to sham treatment: odds ratio 0.54 (95% CI 0.34–0.85; p=0.008) (Figure 2). In a *post hoc* analysis, this finding was also observed when death was excluded, i.e. mRS 0-5 (OR: 0.55 (0.34, 0.91), p=0.019, N=247). When considering the primary outcome, no

differences were found between GTN versus sham in any subgroup of participants with a stroke mimic (Figure 3). In a further *post hoc* analysis, the positive effect of GTN was not localised to any particular type of mimic (Figure 3) or other post hoc subgroups (Additional Figure B).

At the Day 365 follow-up, mRS scores were measured for 279 (94%) stroke mimic patients. Those randomised to the GTN group continued to have a significantly better functional outcome than those in the sham group: OR 0.53 (95% CI 0.33–0.84; p=0.007) (Additional Table G).

Secondary outcomes

Overall, the median length of stay was 4 days [IQR 2, 8] with no significant difference between the GTN and sham groups (Table 2). The course of BP over 4 days of treatment did not reveal any sustained difference between the treatment groups (Additional Figure A). There was no difference for in-hospital interventions (Additional Table H) or neuroimaging results (Additional Table I). The only significant difference between the two groups at 90 days was in the EQ-5D health utility scores (Table 2) with the group randomised to GTN scoring higher than those who received the sham treatment [aMD 0.1; 95% CI 0.0–0.2; p=0.031]. However, this difference was not sustained at Day 365 (Additional Table G).

Safety

There was no difference in the proportion of patients who died in hospital or were discharged to a residential care (Table 2, Figure 4). The causes of death did not differ between GTN and sham (Additional Table J). Similarly, there was no difference in serious adverse events (Additional Table K).

DISCUSSION

Summary of results and comparison with other studies

In our further analysis of the RIGHT-2 study, we found that 26% of the 1149 cases suspected by paramedics to be a stroke had a non-stroke final diagnosis. Patients with a stroke mimic were younger, had less atrial fibrillation, lower BP, fewer FAST positive signs, and a longer onset-to-randomisation compared to those with a confirmed stroke. The most common stroke mimics were neurological conditions; epileptic seizures, migraines and primary headache disorder, and functional neurological illness accounted for almost half of all the cases. The only significant difference between groups at baseline was a lower SBP in the GTN group. At 90 days, patients with stroke mimics had better mRS scores than those with stroke and this finding was maintained in sensitivity analyses and at 365 days. The lack of difference in the rate of serious adverse events between the two groups supports the safety of the GTN intervention among patients with stroke mimic conditions.

These findings add to prior work on prehospital stroke recognition. The rate of 26% stroke mimics is consistent with pooled results for 6,870 patients in physician and paramedic-led EMS systems and larger reviews that included pre and in-hospital settings (6, 17). Our results corroborated previous reports that stroke mimic patients are younger, less likely to display atrial arrhythmias, have a lower BP, and milder stroke signs at presentation compared to stroke patients (5, 18-21). In contrast to earlier findings, we did not observe that mimic patients are more often female, have more vascular risk factors or a history of previous stroke (5, 18-20, 22). The common stroke mimic conditions were similar to those seen in other studies (5, 18-20, 22).

The key but unexpected finding was that 90-day and one-year functional outcomes were better with GTN than the sham. This was despite the absence of any significant demographic or clinical differences between the two treatment groups at baseline (other than SBP), or during their in-hospital care. In addition, the 90-day quality of life score was higher in the GTN group. We suggest several possible explanations.

First, although there were no imbalances in measured prognostic factors between the groups at baseline, there may have been imbalances in unmeasured factors. Second, it is possible that cardiovascular and cerebrovascular events were missed, possibly due to atypical presentation, and included among the mimics. The subgroups with the highest odds of a better outcome with GTN were aged over 80, female, AF, hypertension, previous stroke, normal GCS, and high score on FAST. Third, it is possible that bias in the assessment of outcomes favoured GTN. However, this is unlikely due to the trial design which utilised remote assessment of outcomes at follow-up by a blinded assessor. Fourth, the greater number of deaths among mimic cases who received the sham intervention could have influenced the results. However, a comparison of the 90-day mRS scores for surviving cases was still in favour of GTN and anyway if GTN were effective, it might well reduce death as well as dependence.

Fifth, the results could have been caused by chance, particularly given the small sample size and the moderate rate of non-adherence to the study protocol in the mimic group. Stroke mimic cases in both treatment groups included a wide variety of different neurological and non-neurological diagnoses and it is difficult to explain the effect of GTN across these disorders. Further, EQ-5D differed at day 90 (with a tendency at day 365) in favour of the GTN group, and the point estimate of the BI also favoured the GTN group (although not meeting significance).

Last, the results may reflect an actual treatment effect whereby GTN improves outcome in non-stroke mimics. GTN dilates the blood vessels, increases blood supply and lowers BP due to smooth muscle relaxation. This vasodilatory effect of GTN may improve vasospastic migraine which can present as hemiparesis or hemianopia. The improvement in the seizure group could again be attributed to vasodilation by GTN. Brain oedema has been observed in patients scanned shortly after seizure activity and would cause compression of smaller vessels. Further, NO has generic antimicrobial effects (P Bath, review in preparation) and so might have attenuated the infectious causes of mimic.

This study has direct implications for pre-hospital stroke research. In particular, the frequency of stroke mimic conditions may have an unexpected impact in any intention-to-treat analysis. Mobile stroke units (where available) may still not be the solution with high rates of mimics observed among call-outs (23). Even hospital hyperacute stroke trials are not immune to mimics with 17% of the patients enrolled into the NOR-TEST trial having a final diagnosis of a stroke mimic (24). For now, prehospital trials will need to be designed with the impact of mimics in mind. Developing point of care diagnostics to improve accuracy in selecting the intended trial population of stroke patients is vital (25).

Strengths and limitations

This study used high-fidelity data and the potential for bias was reduced by the limited inclusion criteria and the use of community recruitment. However, at 297 cases, the sample size was relatively small, and some cases were lost to follow-up. We also noted baseline blood pressure differences between the two study groups. Further, the use of simple randomisation may have contributed to potential undetected baseline imbalance. This

approach allowed for rapid randomisation and treatment administration, but future trials could consider using phone or internet-based randomisation in the pre-hospital arena at greater expense.

CONCLUSIONS

Close to a quarter of patients suspected by paramedics to be having an acute stroke are subsequently diagnosed with a non-stroke condition. In this study, it is unclear why administration of transdermal GTN was associated with an improvement in mRS score at 90 days and one year but is likely to represent an undetected baseline imbalance or chance. The lack of difference in the rate of serious adverse events between the two groups supported the safety of GTN intervention in this population with stroke mimic conditions. Future trials should try to improve the discrimination of stroke mimics.

List of abbreviations

BI	Barthel index
BP	Blood pressure
CI	Confidence interval
FAST	Face-Arm-Speech-Time
EQ	European Quality of Life
EQ-5D-3L	European Quality of Life-5 dimensions-3 level
ENOS	Efficacy of Nitric Oxide in Stroke trial
GCS	Glasgow coma scale
GTN	Glyceryl trinitrate
IQR	Inter-quartile range
HSUV	Health status utility value
mmHg	Millimetres of mercury
mRS	Modified Rankin scale
OR	Odds ratio
RIGHT-2	Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2
SBP	Systolic blood pressure
SD	Standard deviation
TIA	Transient ischaemic attack
TICS-M	Telephone Interview for Cognition Scale-modified

UK	United Kingdom
ZDS	Zung depression score

Declarations

Ethics approval and consent to participate

The study was approved by the UK regulator (Medicines and Healthcare products Regulatory Agency, reference: 03057/0064/001–0001; Eudract 2015–000115–40) and national research ethics committee (IRAS: 167115) and was adopted by the National Institute for Health Research Clinical Research Network.

Patients with capacity gave written informed consent to the attending paramedic, that covered the whole trial. If capacity was absent, proxy consent was obtained from an accompanying relative, carer, or friend, if present, or from the paramedic if no accompanying person was present. Confirmatory consent was obtained from the patient, or their relative, carer, or friend in hospital when the patient lacked capacity in the ambulance.

Consent to publish

Not applicable

Availability of data and materials

Individual participant data will be shared with the Virtual International Stroke Trials Archive (VISTA) collaboration. From Jan 1, 2022, the Chief Investigator and Trial Steering Committee will consider other requests to share individual participant data via email at: right-2@nottingham.ac.uk. We will require a protocol detailing hypothesis, aims, analyses, and intended tables and figures. Where possible, we will perform the analyses; if not, de-identified data and a data dictionary will be supplied for the necessary variables for remote analysis. Any sharing will be subject to a signed data access agreement. Ultimately, the data will be published.

Competing interests

PMB is Stroke Association Professor of Stroke Medicine and a National Institute for Health Research (NIHR) Senior Investigator. The views expressed in the article are those of the author(s) and do not necessarily represent those of NIHR or the Department of Health and Social Care. He reports grants from British Heart Foundation during the conduct of the study; personal fees and other fees from Sanofi, Nestlé, DiaMedica, Moleac, Platelet Solutions, Phagenesis, and ReNeuron, outside the submitted work. JMW was supported by the SFC SINAPSE Collaboration (www.sinapse.ac.uk) and reports grants from the British Heart Foundation during the conduct of the study. NSp reports grants from British Heart Foundation, during the conduct of the study. TE reports grants from the British Heart Foundation during the conduct of the study. TR is an NIHR Senior Investigator. All other authors declare no competing interests.

Funding

This work was supported by the British Heart Foundation [grant number CS/14/4/30972] and sponsored by the University of Nottingham. There was no commercial support for the trial, and GTN patches and sham dressings were sourced by the Pharmacy Department at Nottingham University Hospitals NHS Trust. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and two statisticians (LJW, PS) had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Author's contributions

PMB was chief investigator, the lead grant applicant, verified and analysed data and is project guarantor. LJW and PS were the trial statisticians, involved in the design of the trial, and verified and analysed data. MD was the national paramedic lead coordinating ambulance service trial delivery. JMW was a grant applicant and led adjudication of brain scans. NSp was deputy chief investigator and a grant applicant. BT wrote the first draft of this paper. JMW, TE, TR, NSp and PMB were grant co-applicants and participated in the Steering Committee. All authors reviewed and approved the final manuscript.

Acknowledgements

This paper is dedicated to Professor Eivind Berge, MD, PhD, who contributed to the study but did not live long enough to see the results. We thank the patients who participated in this trial and their relatives, the clinical and research teams of the various ambulance services and hospitals, and the paramedics who recruited and treated the patients. We acknowledge support of the English NIHR Clinical Research Network, and that the coordination between multiple ambulance services and hospitals, and large recruitment would not have been possible without NIHR network support. A complete list of the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2) Investigators is provided in the primary publication (10).

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576 **Figure Legends**

577 Table 1. Baseline ambulance and hospital admission characteristics of Mimic patients
578 enrolled in the RIGHT-2 trial. Data are number (%), median [IQR], or mean (standard
579 deviation)
580 AF: atrial fibrillation; bpm: beats per minute; ECG: electrocardiogram; FAST: face-arm-
581 speech test; GTN: glyceryl trinitrate; mmHg: IQR: interquartile range; millimetres of
582 mercury; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale;
583 OCSP: Oxford Community Stroke Project classification; TACS: total anterior circulation
584 stroke

585 Table 2. Primary and main secondary outcomes at days 4 and 90 in participants diagnosed
586 with a stroke mimic. Data are number (%), median [IQR], or mean (standard deviation)
587 aMD: adjusted mean difference; aOR: adjusted odds ratio; CI: confidence interval EQ-5D
588 HUS: EuroQol EQ5D Health utility scores; FAST: face-arm-speech test; GCS: Glasgow
589 Coma Scale; GTN: glyceryl trinitrate; mmHg: millimetres of mercury; MI: multiple
590 imputation; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale;
591 OCSP: Oxford Community Stroke Project classification PP: per protocol analysis; SAE:
592 serious adverse event; TACS: total anterior circulation stroke; TICS-M: Telephone Interview
593 for Cognitive Status -Modified; t-MMSE: modified telephone Mini-Mental State
594 Examination

595 Figure 1. Trial profile for mimic group.

596 Figure 2. Distribution of mRS scores at day 90 for GTN versus sham among 274 stroke
597 mimic participants.
598 Comparison of GTN versus sham, adjusted common odds ratio 0.54 (0.34, 0.85), p=0.008, by
599 ordinal logistic regression, with adjustment for age, sex, pre-morbid modified Rankin Scale,
600 face-arms-speech-time test, pre-treatment SBP, final diagnosis (stroke mimic) and time to

randomisation. The effect of treatment for GTN versus sham is shown as adjusted common odds ratio (acOR).

Figure 3. Forest plot showing modified Rankin Scale, analysed as adjusted ordinal outcome, in subgroup of participants with stroke mimics, with p-value for interaction.

Heterogeneity of the treatment effect on the primary outcome was assessed in by adding an interaction term to an ordinal logistic regression model with adjustment for age, sex, pre-morbid modified Rankin Scale (mRS), face-arm-speech time test, pre-treatment systolic blood pressure (SBP), final diagnosis (stroke mimic) and time to randomisation.

Figure 4. Kaplan-Meier curve for time to death in participants with a stroke mimic, by assigned treatment group.

Comparison of GTN versus sham, adjusted hazard ratio 0.49 (95% confidence intervals 0.20, 1.19), p=0.11, by Cox proportional hazards regression with adjustment for age, sex, pre-morbid modified Rankin Scale, face-arms-speech time test, pre-treatment SBP, final diagnosis (stroke mimic) and time to randomisation.

Additional Files

Additional Table A.

Baseline ambulance and hospital admission characteristics of Mimic versus non-Mimic patients enrolled in the RIGHT-2 trial.

Data are number (%), median [IQR], or mean (standard deviation). Differences in means, medians and proportions are accompanied by 95% confidence intervals.

Additional Table B.

Final diagnosis of mimics.

Data are number (%)

Additional Table C.

Cases whose qualifying event was described as an infection at any time-point (36 participants)

Additional Table D.

Adherence and reasons for non-adherence in GTN versus sham groups.

Data are number (%)

Additional Table E.

Adherence and reasons for non-adherence in mimic versus non-mimic groups.

Data are number (%)

Additional Table F.

Protocol violations

Additional Table G.

Primary and main secondary outcomes at day 365 in all patients with a stroke mimic, except where stated.

Data are number (%), median [IQR], or mean (standard deviation).

Additional Table H.

In-hospital interventions

Additional Table I.

Neuroimaging on admission to hospital and day 2.

Data are number (%), median [IQR], or mean (standard deviation).

Additional Table J.

Causes of death among participants with a stroke mimic

Additional Table K.

Serious adverse events

Additional Figure A.

Blood pressure curves

Additional Figure B.

Forest plot of clinical and imaging information in participants with a stroke mimic

Additional Figure C.

Boxplot of Day 90 mRS, by infection diagnosis (27 participants – one participant with infection is missing their mRS score)

	All	GTN	Sham	Difference	2p
Ambulance data (pre-randomisation)					
Number of patients	297	134	163		
Age (years)	67 (18)	68 (19)	66 (18)	1.7 (-2.4, 5.9)	0.41
< 60 (%)	107 (36)	49 (37)	58 (36)		
60-70 (%)	45 (15)	17 (13)	28 (17)		
70-80 (%)	55 (19)	22 (16)	33 (20)		
>=80 (%)	90 (30)	46 (34)	44 (27)		
Sex (female) (%)	157 (53)	74 (55)	83 (51)	4.3 (-7.1, 15.7)	0.46
Time from onset to randomisation (minutes)	75 [47,126]	72.5 [48,120]	79 [46,140]	-6.0 (-19.0, 5.0)	0.27
ECG, AF/flutter (%)	29 (13)	11 (11)	18 (15)	3.6 (-5.1, 12.3)	0.42
Systolic blood pressure (mmHg)	159 (26)	155 (24)	162 (27)	-7.0 (-12.9, -1.1)	**0.021**
Diastolic blood pressure (mmHg)	91 (16)	89 (16)	92 (16)	-2.7 (-6.4, 1.0)	0.15
Heart rate (bpm)	83 (19)	82 (16)	84 (21)	-1.7 (-5.9, 2.6)	0.44
Glasgow coma scale	14 (2)	14 (2)	14 (2)	-0.3 (-0.7, 0.1)	0.13
Glasgow coma scale <14 (%)	73 (25)	39 (29)	34 (21)	-8.2 (-18.2, 1.8)	0.11
FAST score (/3)	2 (1)	2 (1)	2 (1)	0.0 (-0.1, 0.2)	0.61
FAST score =3 (%)	144 (49)	67 (50)	77 (48)	-2.9 (-14.3, 8.6)	0.63
Hospital admission data (post randomisation)					
Number of patients with data	297	134	163		
Ethnic group, non-white (%)	35 (13)	15 (12)	20 (13)	1.2 (-6.7, 9.0)	0.77
Ethnicity, White (%)	242 (87)	110 (88)	132 (87)		
Ethnicity, Black (%)	14 (5)	5 (4)	9 (6)		
Ethnicity, Asian (%)	18 (6)	10 (8)	8 (5)		
Ethnicity, Other (%)	3 (1)	0 (0)	3 (2)		
Pre-morbid mRS >2 (%)	79 (28)	39 (31)	40 (26)	-4.7 (-15.3, 5.9)	0.38
Medical history (%)					
Hypertension	142 (51)	61 (49)	81 (53)	4.1 (-7.8, 15.9)	0.50
Diabetes mellitus	59 (21)	27 (22)	32 (21)	-0.6 (-10.3, 9.2)	0.91
Previous stroke	85 (31)	37 (30)	48 (32)	2.2 (-8.7, 13.1)	0.70
Ischaemic heart disease	58 (21)	29 (24)	29 (19)	-4.2 (-14.1, 5.6)	0.39
Smoking, current	54 (24)	26 (25)	28 (23)	-2.2 (-13.4, 8.9)	0.69
Antiplatelets	69 (36)	36 (40)	33 (33)	-7.0 (-20.7, 6.7)	0.32
Anticoagulants	33 (17)	15 (17)	18 (18)	1.0 (-9.7, 11.7)	0.86
Either	96 (51)	47 (52)	49 (49)	-3.2 (-17.5, 11.0)	0.66

	All	GTN	Sham	Difference	2p
OCSP syndrome, TACS (%)	40 (18)	15 (16)	25 (19)	3.6 (-6.4, 13.6)	0.49
NIHSS (/42)	4 [2,8]	4 [1,9]	4 [2,7]	0.0 (-1.0, 1.0)	0.64

	N	GTN	Sham	aOR/aMD (95% CI), adjusted	p-value
Day 90 mRS (/6)					
All	274	3 [1,4]	3 [1,4]	0.5 (0.3, 0.9)	**0.008**
Sensitivity analyses					
Per-protocol	245	3 [1,4]	3 [1,4]	0.6 (0.4, 0.9)	**0.026**
With multiple imputation	297	3 [1,4]	3 [1,4]	0.6 (0.4, 0.9)	**0.013**
mean mRS	274	2.5 (1.7)	2.8 (1.9)	-0.5 (-0.8, -0.1)	**0.012**
mRS, unadjusted	274	3 [1,4]	3 [1,4]	0.8 (0.5, 1.2)	0.27
mRS > 2 (%)	274	72 (58.1)	91 (60.7)	0.6 (0.3, 1.2)	0.18
mRS > 2, unadjusted (%)	274	72 (58.1)	91 (60.7)	0.9 (0.6, 1.5)	0.66
mRS, Received thrombolysis	8	1 [1,2]	1 [0,1]	-	-
mRS, No thrombolysis	266	3 [1,4]	3 [1,4]	0.6 (0.4, 0.9)	**0.013**
Admission					
NIHSS (/42)	176	5.7 (6.2)	5.3 (5.3)	-0.2 (-1.8, 1.4)	0.82
FAST (hospital admission) [/3]	186	1.4 (1.1)	1.5 (1.0)	-0.2 (-0.5, 0.1)	0.19
OCSP, TACS (%)	224	15 (15.8)	25 (19.4)	0.8 (0.4, 1.7)	0.57
GCS admission	241	14.4 (1.4)	14.2 (1.8)	0.3 (-0.1, 0.7)	0.13
Day 4 (or discharge)					
Death (%)	279	2 (1.6)	1 (0.6)	2.2 (0.2, 29.8)	0.56
Patients with an SAE (%)	279	6 (4.8)	10 (6.5)	0.8 (0.3, 2.5)	0.73
Infection (%)	275	11 (8.9)	17 (11.3)	0.5 (0.2, 1.2)	0.13
Neurological deterioration (%)	52	2 (7.7)	3 (11.5)	0.1 (0.0, 10.4)	0.27
Neurological deterioration, clinical (%)	275	6 (4.8)	4 (2.6)	2.3 (0.6, 9.4)	0.25
Headache (%)	274	8 (6.5)	8 (5.3)	1.4 (0.5, 4.1)	0.54
Hypotension, SBP <90mmHg (%)	274	3 (2.4)	0 (0)	-	-
Hypertension, SBP >180 mmHg (%)	274	17 (13.8)	15 (9.9)	2.1 (0.9, 4.9)	0.090
Feeding: non-oral (%)	243	7 (6.4)	7 (5.3)	1.1 (0.4, 3.5)	0.87
Glasgow coma scale (/15)	114	14.2 (2.5)	14.2 (2.7)	0.1 (-0.9, 1.1)	0.79
NIHSS (/43)	57	4.5 (10.9)	4.9 (9.7)	-0.6 (-6.4, 5.3)	0.85
Hospital events					
Length of stay (days)	279	4.8 (8.5)	5 (6.9)	-0.6 (-2.4, 1.1)	0.48
Died in hospital (%)	279	6 (4.8)	3 (1.9)	3.7 (0.8, 17.1)	0.098
Died or discharged to institution (%)	271	13 (10.8)	19 (12.6)	0.8 (0.3, 1.7)	0.49
Day 90					
Death (%)	281	8 (6.3)	19 (12.3)	0.5 (0.2, 1.2)	0.11
Disposition (%)	260	1 [1,1]	1 [1,1]	0.6 (0.3, 1.2)	0.14
EQ-5D HUS (/1)	257	0.5 (0.4)	0.5 (0.4)	0.1 (0.0, 0.2)	**0.031**

	N	GTN	Sham	aOR/aMD (95% CI), adjusted	p-value
Quality of life, EQ-VAS (/100)	240	57.3 (25.8)	51.9 (30.3)	6.5 (-0.2, 13.3)	0.057
Barthel Index (/100)	253	75.2 (35.1)	71.7 (39.2)	6.3 (-1.4, 14.0)	0.11
Disability, Barthel index <60 (%)	253	27 (23.9)	33 (23.6)	0.9 (0.4, 1.9)	0.73
TICS-M	112	19.3 (10.5)	15 (11.0)	3.3 (-0.0, 6.5)	0.052
tMMSE	116	15.5 (8.0)	12.7 (9.0)	2.4 (-0.1, 4.9)	0.061
Animal naming	114	14.7 (9.5)	11.8 (10.1)	1.7 (-1.3, 4.7)	0.26
Zung Depression Scale (/100)	139	62.5 (24.3)	62.4 (27.1)	-2.3 (-9.9, 5.3)	0.55
Home time (days)	221	91 (36.2)	85.7 (39.7)	6.3 (-3.0, 15.7)	0.19
Global analysis	112	-	-	-0.1 (-0.2, 0.0)	0.15

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