Glyceryl Trinitrate for Acute Intracerebral Hemorrhage. Results From the Efficacy of Nitric Oxide in Stroke (ENOS) Trial, a Subgroup Analysis

Glyceryl trinitrate for acute intracerebral haemorrhage: results from the Efficacy of Nitric Oxide in Stroke (ENOS) trial, a subgroup analysis

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Keywords

Acute stroke, antihypertensive therapy, blood pressure, glyceryl trinitrate, intracerebral haemorrhage, randomised controlled trial

Abstract

Background and purpose

The Efficacy of Nitric oxide in Stroke (ENOS) trial found that transdermal glyceryl trinitrate (GTN, a nitric oxide donor) lowered blood pressure but did not improve functional outcome in patients with acute stroke. However, GTN was associated with improved outcome if patients were randomised within 6 hours of stroke onset.

Methods

In this pre-specified subgroup analysis, the effect of GTN (5 mg/day for 7 days) versus no GTN was studied in 629 patients with intracerebral haemorrhage presenting within 48 hours and with systolic blood pressure $\geq$140 mmHg. The primary outcome was the modified Rankin Scale (mRS) at 90 days.

Results

Mean blood pressure at baseline was 172/93 mmHg and significantly lower (difference -7.5/-4.2 mmHg; both $p \leq 0.05$) on day 1 in 310 patients allocated to GTN as compared with 319 randomised to no GTN. No difference in the mRS was observed between those receiving GTN versus no GTN (adjusted odds ratio, OR for worse outcome with GTN 1.04, 95% confidence interval (CI) 0.78-1.37; p=0.84). In the subgroup of 61 patients randomised within 6 hours, GTN improved functional outcome with a shift in the modified Rankin Scale (OR 0.22, 95% CI 0.07-0.69, p=0.001). There was no significant difference in the rates of serious adverse events between GTN and no GTN.

Conclusions

In patients with intracerebral haemorrhage within 48 hours of onset, GTN lowered blood pressure, was safe but did not improve functional outcome. Very early treatment might be beneficial but needs assessment in further studies.

Clinical Trial Registration –URL: http://www.isrctn.com/ISRCTN99414122. Unique Identifier: 99414122.

INTRODUCTION

Spontaneous intracerebral haemorrhage (ICH) is a severe form of stroke with more than two-third of survivors disabled at three months and less than one-half surviving the first year.[1] High blood pressure (BP) is common in acute ICH and is associated independently with a worse outcome,[2] in part mediated through expansion of the haematoma.[3, 4] In the large INTERACT-2 trial, intensive BP lowering during the first 6 hours was associated with a trend to improved functional outcome in comparison with guideline BP lowering.[5] In contrast, in a subgroup analysis of patients with acute ICH enrolled into the Scandinavian Candesartan Acute Stroke Trial (SCAST), treatment with oral candesartan was associated with a worse functional outcome.[6] Hence, the management of high BP in acute ICH remains uncertain.

Transdermal glyceryl trinitrate (GTN), a nitric oxide donor is a candidate treatment for acute ICH because it can lower blood pressure without changing cerebral blood flow, has no negative effects on platelet function [7-9] and can be given to patients with dysphagia, a common clinical complication of stroke.[10] The Efficacy of Nitric Oxide in Stroke trial (ENOS) assessed the safety and efficacy of blood pressure lowering with transdermal GTN), in 4,011 patients with acute stroke;[11] nearly one-fifth of these presented with spontaneous ICH.[11] Although the main analysis showed that GTN did not improve death or dependency at 90 days after acute ischaemic stroke or ICH, apparent benefit was observed in patients randomised within 6 hours of stroke onset.[11] This result mirrors a result seen in the pre-hospital pilot Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT) where GTN was administered by paramedics within 4 hours of onset.[10] In this pre-specified analysis,[12] we have further assessed the effect of GTN in the subgroup of patients randomised into the ENOS trial following ICH, both overall (here called ENOS-ICH) and within 6

hours; the time window of 6 hours matches that for recruitment into the INTERACT-2 trial,[5] and encompasses the time window studied in RIGHT.[10]

METHODS

The ENOS trial protocol, statistical analysis plan, baseline data and main results have been published.[11-14] In brief, ENOS compared the effect of transdermal GTN (5 mg daily) versus no GTN, given for one week, in patients with acute stroke (randomisation within 48 hours of ictus) and high systolic blood pressure (systolic BP 140-220 mmHg). Patients taking antihypertensive drugs prior to their stroke were also randomised to continue or stop these temporarily for one week. During treatment, BP was measured daily using a validated automatic BP monitor (Omron 705CP) supplied to each site.[15] The trial was registered (ISRCTN99414122) and approved by the ethics committees and competent authorities in all participating countries as appropriate. Patients or relatives gave consent or proxy consent respectively. In the present analysis, we included all patients enrolled into ENOS with ICH (ENOS-ICH).

Brain imaging

Participants had a baseline CT or MRI scan as part of clinical care, usually before randomisation. Where possible, a second research CT or MRI was performed at day 7+1 (end of treatment). Uncompressed DICOM, JPEG, PNG or GIF image files were sent to the coordinating centre, either uploaded via a secure website or on a CD. Images sent on film were digitised using a VICOM digitiser. Scans were assessed centrally using validated scales by expert neuroradiologists or trained neurologists (AA, LC, AC, JB, RD, PK, JW), for the presence of haemorrhage, its location in the brain, presence and amount of mass effect, presence of blood in the subarachnoid space or ventricles, and underlying changes in the brain including cerebral atrophy,[16] leukoaraiosis,[16] and presence of old lesions.

Haematoma volume (measured manually by ABC/2 formula [17] using Osirix software [18] on a 26 inch Apple iMac), shape and density (using an ordered 5-point categorical scale),[19] shape index (perimeter of haematoma/4∏ x area),[20] density index (standard deviation/mean attenuation),[21] and presence of blood in the subarachnoid space or ventricles using the Graeb score and its modified version [22, 23] were also measured. All imaging assessments were performed by KK masked to clinical data and treatment assignment.

Outcomes

The primary outcome was functional outcome assessed using the modified Rankin Scale (mRS) at 90 days after randomisation. Secondary outcomes studied at day 90 included activities of daily living (Barthel Index, BI [24]); cognition (modified telephone Mini-Mental State Examination, t-MMSE [25]); and Telephone Interview for Cognition Scale, (TICS-M [26]); health-related quality of life (European Quality of Life-5 dimensions-3 level, EQ-5D,[27] from which health utility status, HUS, was calculated [28] and mood (short Zung Depression Score, ZDS [29]). Safety outcomes comprised all-cause mortality and case-specific fatality, early neurological deterioration (defined as a decrease of at least 5 points or decrease in consciousness of more than 2 points from baseline to day 7 on the Scandinavian Stroke Scale, SSS), recurrent stroke by day 7, symptomatic hypotension, hypertension,[11] and serious adverse events. Outcomes at day 90 were assessed via telephone by trained investigators at national coordinating centres who were masked to treatment allocation.

Analyses

Statistical analysis was performed by intention-to-treat and followed the trial's statistical analysis plan and analysis approaches used in the primary publication.[11, 12] Analyses were performed for all patients with ICH in ENOS, and separately for those

with ICH who were randomised within 6 hours of onset. Data are shown as number (%), median [interquartile range], or mean (standard deviation). Patients who died were allocated an extreme score: -5: Barthel Index; EQ-VAS -1: EQ-VAS, SSS 0, t-MMSE, TICS-M, verbal fluency; 0: health utility status (derived from EQ-5D); 6: mRS and 102.5: Zung Depression Scale.[11, 30] Comparisons between the treatment groups were performed with binary logistic regression, ordinal logistic regression, Cox proportional regression, or multiple linear regression. Statistical models were adjusted for prognostic baseline covariates: age, systolic BP, SSS score, time from symptom onset to randomisation, haematoma volume and treatment assignment (GTN vs no GTN). Odds ratio, hazard ratio or mean difference, with 95% confidence intervals, are given and statistical significance was set at $p \leq 0.05$. Heterogeneity of treatment effect was assessed by including an interaction term in adjusted models. Analyses were performed using SPSS (version 21) on an Apple Mac.

RESULTS

Baseline characteristics

Between July 2001 and October 2013, a total of 629 participants with ICH were enrolled in the trial; 310 participants were randomly assigned to receive GTN and 319 participants to no GTN (Table 1). Baseline characteristics were well matched between the two groups. The average age was 67 years; 66% of patients were male; 54% were enrolled from the UK; mean time from onset to recruitment 25 hours; and mean stroke severity 30.5 (s.d.12.4) on the Scandinavian Stroke Scale (SSS), equivalent to National Institute of Health Stroke Scale (NIHSS) 12.6 (5.3).[31]

A majority (71%) of patients had their baseline scans performed within 12 hours of onset (Table 1). 87% of haemorrhages were deep-seated in the lacunar and striato-capsular brain regions, most haematomas (63%) caused mass effect (moderate or extreme swelling), and many (67%) patients had leukoaraiosis. Evidence of a previous stroke was present in 50% of patients and brain atrophy was seen in 62% of the available scans. The mean haematoma volume was 13.3 cm^3, and 153 (26%) of patients had an intraventricular haemorrhage (IVH). Additional information on baseline neuroimaging is given in Supplementary Table I.

Blood pressure

Mean BP at baseline was 172.1/93.4 mmHg and fell in both treatment groups over the first week. Following the first dose of GTN versus no GTN, BP was significantly lower by 7.5/4.2 mmHg (p=0.02/0.05 respectively); BP did not differ thereafter (Supplementary Figure I).

Clinical outcomes

At day 90, the median mRS was 3 [IQR 2] in both the GTN and no GTN groups and did not differ in an adjusted analysis, common OR 1.04 (0.78-1.38) (Table 2, Figure 1) or unadjusted analysis (data not shown). A test of 'goodness-of-fit' showed that the assumption of proportional odds was not violated (p=0.09). When assessed in subgroups defined by baseline clinical or neuroimaging factors, there were significant interactions between treatment and mRS for time to randomisation and stroke subtype (Supplementary Figures II and III).

The cumulative risk of all causes of death during follow up did not differ between GTN and no GTN (adjusted hazard ratio 1.02, 95% CI 0.67-1.56, p=0.92; Supplementary Figure IV). There were no significant differences between the two groups in any of the secondary outcomes studied at days 7 or 90, including measures of disability, cognition, mood and quality of life (Table 2). The number of patients with a serious adverse event during follow-up did not differ between the treatment groups (24.2% vs. 21.9%, p=0.50) (Supplementary Table II).

Relationship between baseline neuroimaging and mRS at day 90

Table 3 shows the association between baseline neuroimaging characteristics and the primary outcome of mRS. Imaging measures that were significantly associated with outcome on both univariate and co-variate-adjusted analyses comprised the presence of intraventricular haemorrhage or atrophy, irregular haematoma shape and heterogeneous density.

Patients randomised within 6 hours

Of the 629 patients with ICH, 61 (9.7%) participants were randomised within 6 hours; the average time to treatment was 4.4 (1.2) hours (Table 1). Patients were less likely to be enrolled in Asia or other non-UK countries, had a larger initial haemorrhage volume (mean 16.9 cm3) and were more likely to have IVH.

Patients randomised to GTN (versus no GTN) had less impairment (higher SSS) at day 7, and were less likely to die in hospital (Table 2). At day 90, GTN was associated with an improved functional outcome assessed using the mRS, manifest as a shift to less dependency (Table 2, Figure 2). Similarly, participants randomised to GTN were less disabled and had significantly better quality of life, mood and cognition scores (Table 2). A trend to a reduction in death was seen in those patients randomised to GTN versus no GTN. (adjusted hazard ratio 0.19, 95% CI 0.03-1.01, p=0.0.

Effect of GTN on haemorrhage measures at day 7

One hundred and eighty-one patients had repeat brain imaging at one week for an assessment of the effect on haemorrhage characteristics (Table 4). Of these, 93 patients received GTN and 88 to no GTN. When adjusted for baseline value, treatment with GTN was associated with a smaller reduction in haematoma volume (mean difference -4.3 cm^3; p=0.06).

DISCUSSION

In this subgroup of patients enrolled into the ENOS trial with ICH, functional outcome (assessed using the mRS) did not improve with GTN as compared to no GTN. This result mirrors that across the main study and is in spite of GTN reducing BP by 7.5/4.2 mmHg. Further, no benefit was seen in key secondary outcomes, including activities of daily living, cognition, mood and quality of life. The absence of significant differences in the rates of deaths or serious adverse events between the two treatment groups suggests that treatment with GTN is safe. In a pre-specified analysis of the effect of treatment in patients randomised within 6 hours of ICH onset, GTN reduced early impairment; late dependency, disability, and death; and improved late cognition, mood and quality of life.

These findings may have a number of explanations. First, patients could be randomised up to 48 hours after stroke onset. The large INTERACT-2 trial suggested that intensive BP lowering might be effective in patients enrolled within 6 hours [5] so the time window for recruitment into ENOS (mean 25.1 hours, maximum 48 hours) may have been too long. Supporting this is the observation that patients randomised within 6 hours of the onset of ICH into ENOS appeared to benefit with less dependency, disability, impairment and mood disturbance, and better cognition and quality of life. Very early BP lowering might help limit haematoma expansion.[32, 33] Second, the degree by which BP was lowered may have been too small; INTERACT-2 achieved a reduction of 14 mmHg by 6 hours and showed a near-significant effect on functional outcome.[5] Last, the duration of BP control in ENOS-ICH was limited to 3 days as tachyphylaxis developed, a known feature of organic nitrate therapy. Nevertheless, these explanations are confounded by results from the subgroup of

patients with ICH randomised into the large SCAST trial,[6] where oral candesartan was associated with a worse functional outcome.[6] Here, treatment could be started up to 30 hours after stroke onset and the difference in BP between active and placebo groups was smaller than in ENOS-ICH at 6.3/3.3 mmHg.

The reduction in ICH volume in the GTN group (4 cm^3) was similar to the effect observed in trials of rFVIIa although the agent was tested in earlier time windows.[34, 35] Mechanisms by which nitric oxide donors might reduce haematoma volume, and improve functional outcome if given early, include lowering BP, neuroprotection, and improving collateral blood flow. The latter two effects have been seen in experimental models of brain ischaemia[36, 37] and may be of relevance after ICH.

This subgroup analysis of ENOS has a number of strengths including recruitment of patients with ICH from multiple ethnic groups across five continents over a wide time window representative of routine clinical practice. Baseline neuroimaging and clinical outcomes were assessed masked to treatment assignment,[13] follow-up was near complete,[11] and the analysis was pre-specified.[12] However, exclusion of patients with low or normal BP (systolic BP <140 mmHg) or very high (>220 mmHg), those with reduced consciousness (GCS<8), and those without motor signs, may have limited the external validity of the findings and especially the number of patients with large haematoma.

In conclusion, this subgroup analysis of ENOS was neutral and did not identify any beneficial effect or harm in lowering BP with GTN in patients with acute ICH. Transdermal GTN appears to be safe and modestly effective in lowering BP in acute ICH, which can be useful in patients who are unable to swallow. The results in those patients randomised within 6 hours of ICH onset and recent guidelines [38, 39] support

ongoing or planned trials of lowering BP in the ultra-acute and hyper-acute periods after stroke, including the ATACH-2 trial of intravenous nicardipine,[40] and RIGHT-2 trial of GTN administered in the pre-hospital phase of stroke (ISTRCTN26986053).

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DISCLOSURES

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Table 1. Baseline clinical and neuroimaging characteristics of all patients with intracerebral haemorrhage and those randomised within 6 hours. Data are number (%), median [interquartile range], or mean (standard deviation). Comparison of patients randomised within 6 hours versus those randomised later by Fisher's exact test, Mann-Whitney U test or t test.

	All	GTN	No GTN	All ≤6 hours	GTN	No GTN	2p
Clinical characteristics							
Number of patients (N)	629	310	319	61	29	32	-
Age (years)	67.0 (12.4)	66.6 (12.0)	67.5 (12.7)	69.6 (12.5)	68.3 (11.4)	70.8 (13.5)	0.12
Sex, male (%)	415 (66.0)	217 (70.0)	198 (62.1)	38 (62.3)	16 (55.2)	22 (68.8)	0.56
Premorbid mRS>0 (%)	143 (22.7)	66 (21.3)	77 (24.1)	12 (19.7)	5 (17.2)	7 (21.9)	0.58
Country (%)							
UK	337 (53.6)	170 (54.8)	167 (52.4)	35 (57.4)	18 (62.1)	17 (53.1)	0.57
Asia	179 (28.5)	87 (28.1)	92 (28.8)	8 (13.1)	2 (6.9)	6 (18.8)	0.010
Other	113 (18.0)	53 (17.1)	60 (18.8)	18 (29.5)	9 (31.0)	9 (28.1)	0.028
Time to randomisation (hours)	25.1 (13.0)	25.2 (13.1)	25.1 (12.9)	4.4 (1.2)	4.5 (1.1)	4.4 (1.3)	-
<6 hours (%)	61 (9.7)	29 (9.4)	32 (10.0)	-	-	-	-

Smoking, current (%)	124 (20.4)	58 (19.3)	66 (21.4)	11 (18.0)	8 (27.6)	3 (9.4)	0.84
Treated hypertension (%)	253 (40.2)	121 (39.0)	132 (41.4)	17 (27.9)	8 (27.6)	9 (28.1)	0.06
Previous stroke (%)	79 (12.6)	41 (13.2)	38 (11.9)	10 (16.4)	6 (20.7)	4 (12.5)	0.39
Ischaemic heart disease (%)	58 (9.2)	29 (9.4)	29 (9.1)	5 (8.2)	3 (10.3)	2 (6.3)	0.86
Atrial fibrillation (%)	42 (6.7)	18 (5.8)	24 (7.5)	2 (3.3)	1 (3.4)	1 (3.1)	0.30
Diabetes mellitus (%)	81 (12.9)	44 (14.2)	37 (11.6)	9 (14.8)	3 (10.3)	6 (18.8)	0.68
TACS (%)	217 (34.5)	105 (33.9)	112 (35.1)	22 (36.1)	10 (34.5)	12 (37.5)	0.81
SSS (/58)	30.5 (12.4)	30.1 (12.7)	30.9 (12.1)	30.1 (11.1)	30.3 (11.4)	30.0 (10.9)	0.81
NIHSS (/42), calculated [31]	12.6 (5.3)	12.7 (5.5)	12.4 (5.2)	12.7 (4.8)	12.7 (4.9)	12.8 (4.7)	0.81
Glasgow Coma Scale [/15]	15.0 [1.0]	15.0 [1.0]	15.0 [1.0]	15.0 [1.0]	15.0 [1.0]	15.0 [1.0]	0.43
Blood pressure (mmHg)							
Systolic	172.1 (19.4)	172.3 (18.9)	171.8 (19.9)	172.4 (16.8)	174.4 (19.2)	170.6 (14.4)	0.90
Diastolic	93.4 (13.9)	94.0 (13.1)	92.7 (14.6)	95.7 (12.2)	96.9 (13.4)	94.7 (11.1)	0.19
Heart rate (bpm)	77.9 (14.5)	78.0 (14.6)	77.8 (14.4)	76.7 (13.6)	75.6 (15.5)	77.8 (11.8)	0.54
Neuroimaging characteristics							
Available scan	587 (93.3)	296 (95.5)	291 (91.2)	57 (93.4)	28 (96.6)	29 (90.6)	0.89
Time, onset-neuroimaging (%)							

≤12 hours	414 (70.5)	220 (74.3)	194 (66.7)	53 (93.0)	27 (96.4)	26 (89.7)	0.78
>12 hours	173 (29.5)	76 (25.7)	97 (33.3)	4 (7.0)	1 (3.6)	3 (10.3)	0.50
Adjudicated findings							
Haematoma location (%)							
Lobar or cerebellar †	79 (13.5)	42 (14.2)	37 (12.7)	12 (21.1)	7 (25.0)	5 (17.2)	0.76
Deep ‡	508 (86.5)	254 (85.8)	254 (87.3)	45 (78.9)	21 (75.0)	24 (82.8)	0.75
Mass effect (%)							
No swelling or mild swelling	218 (37.2)	107 (36.3)	111 (38.1)	22 (38.6)	11 (39.3)	11 (37.9)	1.00
Moderate to severe swelling	299 (50.9)	155 (52.4)	144 (49.5)	28 (49.1)	14 (50.0)	14 (48.3)	0.90
Extreme swelling	70 (11.9)	34 (11.5)	36 (12.4)	7 (12.3)	3 (10.7)	4 (13.8)	1.00
Leukoaraiosis (%)	391 (66.6)	199 (67.2)	192 (66.0)	38 (66.7)	19 (67.9)	19 (65.5)	1.00
Previous stroke lesion (%)	291 (49.6)	149 (50.3)	142 (48.8)	33 (57.9)	18 (64.3)	15 (51.7)	0.21
Atrophy (%)	366 (62.3)	186 (62.8)	180 (61.9)	40 (70.2)	19 (67.9)	21(72.4)	0.79
Measured CT scan findings							
Volume, ABC/2 (cm3)	13.3 (16.5)	13.2 (15.3)	13.3 (17.7)	16.9 (30.5)	13.0 (14.4)	20.8 (40.7)	0.09
With IVH (n=151, 25.7%)							
Volume, ABC/2 (cm3)	18.5 (23.6)	17.7 (18.3)	19.2 (27.8)	31.8 (52.2)	21.1 (20.6)	40.1 (67.9)	0.018

IVH Volume (ml)	4.8 (7.3)	4.2 (5.0)	5.4 (9.0)	7.2 (6.2)	7.1 (5.7)	7.3 (6.8)	0.18
Shape index[20]	2.4 (3.7)	2.2 (1.9)	2.6 (4.8)	3.2 (2.1)	3.3 (2.9)	3.2 (1.5)	0.35
Density index[21]	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.3 (0.1)	0.006
Graeb score (/12) [22]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 5.0]	4.0 [2.5, 6.0]	4.0 [2.0, 6.0]	4.0 [3.0, 6.0]	0.047
Without IVH (n=436, 74.3%)							
Volume, ABC/2 (cm3)	11.4 (12.6)	11.7 (13.9)	11.1 (11.2)	11.0 (11.8)	10.3 (11.1)	11.7 (12.9)	0.87
Shape index [20]	1.2 (1.1)	1.2 (1.2)	1.2 (1.0)	1.4 (1.1)	1.3 (0.9)	1.5 (1.3)	0.73
Density index [21]	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.0)	0.2 (0.1)	0.52

bpm: beats per minute; ICH: intracerebral haemorrhage; IVH: intraventricular haemorrhage; MCA: middle cerebral artery; mRS: modified Rankin scale; NIHSS: National Institute of Health Stroke scale; SSS: Scandinavian Stroke Scale; TACS: total anterior circulation syndrome.

† Lobar: borderzone regions, cerebellar and or brainstem, ACA, PCA territory and MCA territory excluding striatocapsular regions

‡ Deep: lacunar, MCA territory including striatocapsular regions

Shape index was calculated as perimeter of haematoma/4∏ x surface area.[20] Density index was determined as standard deviation/mean Hounsfield attenuation unit.

Table 2. Secondary outcomes at day 7 and day 90 for all patients with intracerebral haemorrhage and those randomised within 6 hours. Data are number (%), mean (standard deviation) with 95% confidence intervals. Data are number of patients (%), mean (standard deviation) or median [interquartile range]. Comparison by logistic regression, ordinal regression or multiple regression with adjustment for age, sex, pre-morbid mRS, history of previous stroke, history of diabetes, severity, total anterior circulation syndrome, volume of intracerebral haemorrhage, systolic blood pressure, feeding status and time to randomisation.

Outcome	N	GTN	No GTN	OR/MD (95% CI)	2p	≤6 hours	GTN	No GTN	OR/MD (95% CI)	2p
Patients	629	310	319			61	29	32		
Day 7 (or discharge)	627	310	317							
Death (%)	627	10 (3.2)	10 (3.2)	1.03 (0.38, 2.88)	0.95	60	2 (6.9)	4 (12.5)	-	1.00
SSS (/58)	625	34.5 (15.4)	34.8 (16.0)	0.18 (-1.30, 1.69)	0.80	60	33.4 (16.4)	27.1 (19.6)	7.0 (1.0, 13.1)	0.033
Recurrence (%)	626	8 (2.6)	4 (1.3)	2.43 (0.63, 9.29)	0.19	60	0	1 (3.1)	-	1.00

Outcome	N	GTN	No GTN	OR/MD (95% CI)	2p	≤6 hours	GTN	No GTN	OR/MD (95% CI)	2p
Hospital events	623	308	315			59	29	30		
Died in hospital (%)	623	28 (9.0)	32 (10.2)	0.92 (0.48, 1.76)	0.79	59	2 (6.9)	9 (30.0)	-	-
Death or discharge to institution (%)	623	121 (39.3)	131 (41.6)	0.84 (0.59, 1.22)	0.37	59	14 (48.3)	14 (46.7)	1.20 (0.32, 4.43)	0.79
Day 90	623	309	316			61	29	32		
Death (%)	625	42 (13.6)	47 (14.9)	0.91 (0.55, 1.55)	0.76	61	2 (6.9)	12 (37.5)	†	0.006
mRS (/6)	625	3 [2]	3 [2]	1.04 (0.78, 1.38)	0.81	61	3 [2]	4 [4]	0.19 (0.06, 0.59)	0.004
Barthel Index	622	62.3 (38.1)	61.4 (39.7)	1.26 (-3.65, 6.17)	0.62	61	66.9 (36.4)	46.9 (45.7)	20.71 (6.34, 35.07)	0.005
t-MMSE	369	10 (7.2)	10.1 (7.4)	0.04 (-1.20, 1.28)	0.95	38	11.9 (6.4)	6.5 (8.3)	3.38 (-0.29, 7.10)	0.008
TICS-M	370	11.9 (9.3)	12.7 (9.3)	-0.64 (-2.20, 0.93)	0.43	39	16.6 (9.1)	7.1 (9.3)	7.17 (2.20, 12.12)	0.005

Outcome	N	GTN	No GTN	OR/MD (95% CI)	2p	≤6 hours	GTN	No GTN	OR/MD (95% CI)	2p
Animal naming (/∞)	376	8.2 (7.8)	7.9 (7.4)	0.28 (-1.09, 1.65)	0.69	39	12.8 (8.0)	4.8 (7.3)	7.92 (2.93, 12.92)	<0.001
ZDS (/100)	516	60.1 (24.2)	59.6 (24.3)	0.62 (-3.12, 4.43)	0.73	50	54.2 (20.6)	71.8 (28.6)	-17.58 (-32.25, -3.01)	<0.001
HUS (/1)	621	0.45 (0.31)	0.46 (0.32)	-0.01 (-0.05, 0.03)	0.60	61	0.53 (0.3)	0.53 (0.32)	0.19 (0.06, 0.32)	0.003
EQ-VAS (/100)	543	54.6 (31.3)	55.1 (31.5)	-0.44 (-5.16, 4.27)	0.85	57	60.9 (26.7)	40.4 (38.1)	21.28 (6.31, 36.25)	0.005
Dead or institution (%)	616	97 (31.4)	92 (29.1)	1.09 (0.72, 1.67)	0.68	61	13 (44.8)	14 (43.8)	0.51 (0.12, 2.18)	0.36

BI: Barthel Index; EQ-VAS: EQ-Visual Analogue Scale; HUS: health utility status; ICH: intracranial haemorrhage; mRS: modified Rankin Scale; t-MMSE: Modified telephone Mini-Mental State Examination; SAE: serious adverse event; SBP: systolic blood pressure; SSS: Scandinavian Stroke Scale; TICS-M: Modified Telephone Interview for Cognitive Status; ZDS: Zung Depression Scale. † Fisher's exact test

Table 3. Relationships between baseline imaging characteristics and functional outcome (modified Rankin Scale) at day 90. Results are odds ratio or mean difference with 95% confidence interval with comparison by logistic regression, ordinal regression or multiple regression; results are unadjusted, and adjusted for age, sex, severity (Scandinavian Stroke Scale) and time from stroke onset to imaging.

Haematoma characteristics	Univariate analyses OR/MD (95% CI)	2p	Co-variate adjusted OR/MD (95% CI)	2p
Haematoma location				
Lobar	1.32 (0.87, 2.00)	0.19	1.31 (0.85, 2.03)	0.22
Deep	1.08 (0.76, 1.53)	0.68	0.84 (0.58, 1.21)	0.35
Side of the brain				
Left	0.89 (0.67, 1.37)	0.40	0.76 (0.57, 1.01)	0.18
Right	1.10 (0.83, 1.45)	0.50	1.29 (0.97, 1.71)	0.09
Bilateral	2.41 (0.51, 11.50)	0.50	2.50 (0.41, 15.35)	0.32
Mass effect	2.30 (1.61, 3.29)	<0.0001	1.35 (0.93, 1.96)	0.18

Leukoaraiosis	2.14 (1.58, 2.90)	<0.0001	1.34 (0.96, 1.86)	0.09
Subarachnoid haemorrhage	2.22 (1.50, 3.28)	<0.0001	1.47 (0.97, 2.21)	0.07
Intraventricular haemorrhage	2.61 (1.86, 3.67)	<0.0001	1.92 (1.35, 2.74)	<0.0001
Previous stroke lesion	1.19 (0.90, 1.59)	0.23	1.18 (0.88, 1.59)	0.28
Remote haemorrhage	5.21 (1.11, 24.57)	0.04	1.39 (0.20, 9.03)	0.75
Cerebral atrophy	2.70 (1.99, 3.66)	<0.0001	1.46 (1.14, 1.86)	0.002
Volume ABC/2 (cm3)	1.02 (1.01, 1.03)	<0.0001	1.01 (0.99, 1.02)	0.56
Largest measured diameter (cm)	1.12 (1.07, 1.32)	<0.001	0.88 (0.74, 1.04)	0.14
Largest visual diameter	2.52 (1.69, 3.76)	<0.0001	1.24 (0.81, 1.89)	0.32
Haemorrhage shape (/5)	1.36 (1.23, 1.51)	<0.0001	1.28 (1.15, 1.42)	<0.0001
Haemorrhage density (/5)	1.42 (1.27, 1.60)	<0.0001	1.27 (1.13, 1.42)	<0.0001

Haematoma characteristics	Univariate analyses OR/MD (95% CI)	2p	Co-variate adjusted OR/MD (95% CI)	2p
Shape index	1.04 (0.98, 1.12)	0.22	1.03 (0.96, 1.11)	0.38
Density index	1.00 (1.00, 1.01)	0.24	1.00 (0.99, 1.01)	0.45
Haemorrhages with IVH				
Volume (ABC/2 cm3)	1.01 (0.99, 1.02)	0.19	1.00 (0.97, 1.03)	0.94
IVH volume (cm3)	1.02 (0.98, 1.06)	0.40	1.01 (0.97, 1.06)	0.56
Haemorrhage shape (/5)	1.31 (1.03, 1.67)	0.026	1.42 (1.11, 1.82)	<0.0001
Haemorrhage density (/5)	1.69 (1.37, 2.11)	<0.0001	1.49 (1.19, 1.86)	<0.0001
Graeb score (12)	1.07 (0.94, 1.22)	0.31	1.03 (0.90, 1.18)	0.67
Modified Graeb score (32)	1.03 (0.96, 1.10)	0.45	1.00 (0.94, 1.08)	0.80
Shape index	0.98 (0.91, 1.06)	0.63	0.99 (0.92, 1.08)	0.89
Density index	1.00 (1.00, 1.00)	0.13	1.00 (0.99, 1.00)	0.63

Table 4. Effect of treatment on neuroimaging measures at day 7 in 181 patients with a baseline scan prior to randomisation, for all patients with intracerebral haemorrhage. Data are number (%), median [interquartile range], or mean (standard deviation), and odds ratio or mean difference with 95% confidence intervals. Comparison by logistic regression, ordinal regression or multiple regression with adjustment for baseline value.

Scan variables		All	Adjusted	
	GTN	No GTN	OR/MD (95% CI)	2p
Haematoma location	93	88		
Lobar (%)	10 (10.8)	11 (12.5)	1.24 (0.49, 3.15)	0.66
Deep (%)	83 (89.2)	77 (42.5)	0.63 (0.10, 3.85)	0.61
Intraventricular haemorrhage (%)	25 (26.9)	19 (21.6)	0.85 (0.43, 1.70)	0.65
Subarachnoid haemorrhage (%)	7 (7.5)	11 (12.5)	0.50 (0.17, 1.49)	0.21
Mass effect (%)	79 (84.9)	81 (92.0)	1.04 (0.72, 1.50)	0.84
Brain tissue reduction (%)	53 (57.0)	59 (67.0)	0.51 (0.24, 1. 10)	0.09
Cortical atrophy (%)	44 (47.3)	42 (47.7)	1.26 (0.47, 3.36)	0.64

Scan variables	All		Adjusted	
	GTN	No GTN	OR/MD (95% CI)	2p
Central atrophy (%)	48 (51.6)	58 (65.9)	0.92 (0.60, 2.10)	0.73
Leukoaraiosis (%)	64 (68.8)	63 (71.6)	0.83 (0.37, 1.87)	0.66
Previous stroke lesion (%)	41 (44.1)	51 (60.0)	0.57 (0.28, 1.16)	0.12
Visual longest diameter (cm)			0.66 (0.34, 1.27)	0.21
<3	38 (40.1)	36 (40.9)		
3-5	46 (49.5)	28 (31.8)		
5-8	6 (6.5)	20 (22.7)		
>8	3 (3.2)	4 (4.5)		
Volume ABC/2 (cm3)	15.4 (16.0)	19.2 (21.4)	-4.30 (-8.78, 0.23)	0.06
Largest measured diameter	3.6 (1.3)	3.8 (1.6)	-0.04 (-0.33, 0.25)	0.81
Shape index	1.7 (0.8)	1.7 (1.0)	-0.04 (-0.31, 0.24)	0.80
Shape [/5]	2 [2,3]	2 [1,3]	0.14 (-0.19, 0.47)	0.41
Density index	0.4 (0.7)	0.3 (0.5)	0.10 (-0.07, 0.28)	0.27
Density [/5]	2 [1,3]	2 [1,3]	0.12 (-0.18, 0.43)	0.43

Scan variables		All	Adjusted	
	GTN	No GTN	OR/MD (95% CI)	2p
No IVH (n=137)				
Volume ABC/2(cm3)	14.7 (15.3)	18.4 (18.4)	-4.52 (-9.05, 0.01)	0.05
Shape index	1.5 (0.6)	1.7 (1.0)	-0.12 (0.42, 0.17)	0.42
Shape [/5]	2 [1,3]	2 [2,3]	0.04 (-0.31, 0.39)	0.82
Density index	0.4 (0.9)	0.3 (0.7)	0.15 (-0.11, 0.41)	0.26
Density [/5]	2 [1,3]	2 [1,3]	0.34 (-0.03, 0.71)	0.07
With IVH (n=44)				
Volume ABC/2(cm3)	17.1(17.9)	18.4 (17.4)	-0.64 (-8.53, 7.24)	0.87
IVH volume (cm3)	3.0 (6.0)	3.7 (5.9)	0.52 (-4.96, 6.01)	0.85
Shape index	2.0 (1.0)	2.1 (1.2)	-0.12 (-0.79, 0.55)	0.73
Shape [/5]	4 [3,5]	4 [3,5]	1.00 (0.50, 1.99)	0.99
Density index	0.3 (0.1)	0.3 (0.1)	-0.01 (-0.06, 0.04)	0.66
Density [/5]	2 [1,3]	2 [1,3]	0.00 (-0.64, 0.63)	1.00

Scan variables		All	Adjusted	
	GTN	No GTN	OR/MD (95% CI)	2p
Graeb score	2.9 (1.8)	2.1 (1.3)	0.94 (-0.25, 2.12)	0.12
Modified Graeb score	3.4 (2.7)	2.5 (2.2)	1.23 (-0.59, 3.05)	0.18

Figure 1. Distribution of modified Rankin scores for all 625 patients with intracerebral haemorrhage at day 90: glyceryl trinitrate versus no glyceryl trinitrate. Comparison by ordinal logistic regression adjusted for age, sex, premorbid mRS, history of previous stroke, history of diabetes, total anterior circulation syndrome, systolic blood pressure, feeding status, time to randomisation, and allocation to continue or stop pre-stroke antihypertensive drugs. Adjusted common odds ratio 1.04 (95% CI 0.78, 1.38), p=0.81.

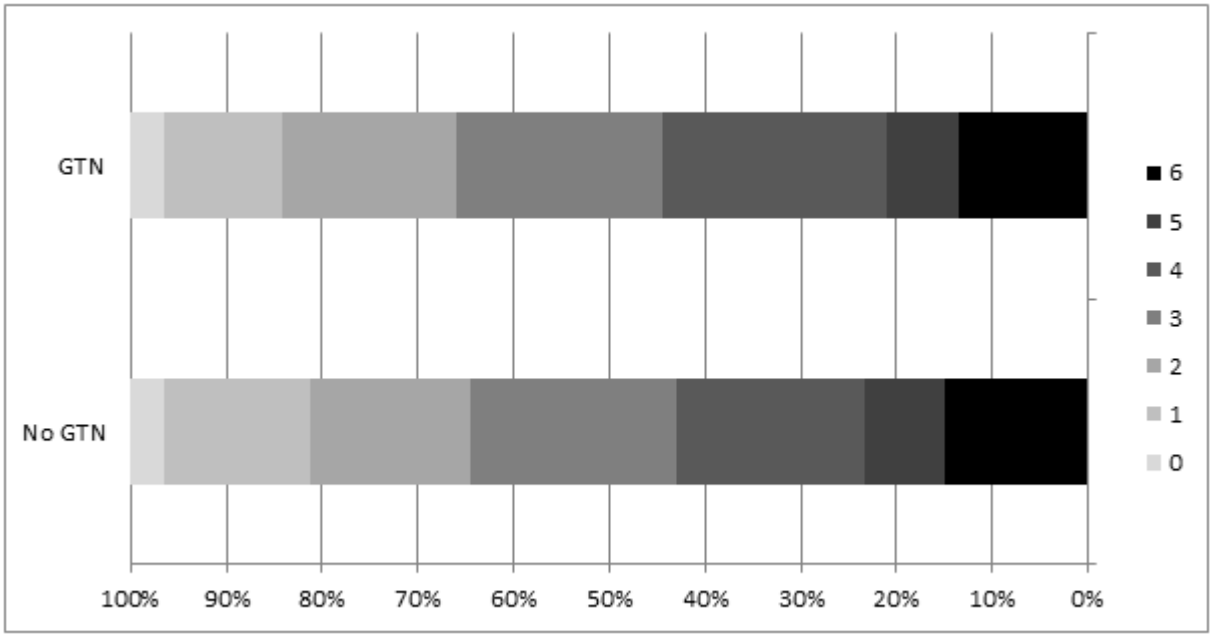

Figure 2. Distribution of modified Rankin scores for patients randomised within 6 hours at day 90: glyceryl trinitrate (n=29) versus no glyceryl trinitrate (n=32). Comparison by ordinal logistic regression adjusted for age, sex, premorbid mRS, history of previous stroke, history of diabetes, total anterior circulation syndrome, systolic blood pressure, feeding status, time to randomisation, and allocation to continue versus stop pre-stroke antihypertensive drugs. Adjusted common odds ratio 0.19 (95% CI 0.06, 0.59), p=0.004.