Glyceryl Trinitrate for Acute Intracerebral Hemorrhage

Results From the Efficacy of Nitric Oxide in Stroke (ENOS) Trial, a Subgroup Analysis

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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 randomized within 6 hours of stroke onset.

Methods—In this prespecified subgroup analysis, the effect of GTN (5 mg/d for 7 days) versus no GTN was studied in 629 patients with intracerebral hemorrhage presenting within 48 hours and with systolic blood pressure ≥140 mm Hg. The primary outcome was the modified Rankin Scale at 90 days.

Results—Mean blood pressure at baseline was 172/93 mm Hg and significantly lower (difference −7.5/−4.2 mm Hg; both $P \leq 0.05$) on day 1 in 310 patients allocated to GTN when compared with 319 randomized to no GTN. No difference in the modified Rankin Scale was observed between those receiving GTN versus no GTN (adjusted odds ratio for worse outcome with GTN, 1.04; 95% confidence interval, 0.78–1.37; $P=0.84$). In the subgroup of 61 patients randomized within 6 hours, GTN improved functional outcome with a shift in the modified Rankin Scale (odds ratio, 0.22; 95% confidence interval, 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 hemorrhage 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.

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Spontaneous intracerebral hemorrhage (ICH) is a severe form of stroke with more than two-third of survivors disabled at 3 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 hematoma.[3,4] In the large Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT-2) 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 BP 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 (ENOS) trial assessed the safety and efficacy of BP lowering with transdermal GTN in 4011 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 ischemic stroke or ICH, apparent benefit was observed in patients randomized within 6 hours of stroke onset.[11] This result mirrors a result seen in the prehospital 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 prespecified analysis,[12] we have further assessed the effect of GTN in the subgroup of patients randomized into the ENOS trial after 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 1 week, in patients with acute stroke (randomization within 48 hours of ictus) and high systolic BP (140–220 mm Hg). Patients taking antihypertensive drugs before their stroke were also randomized to continue or stop these temporarily for 1 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 computed tomographic or magnetic resonance imaging scan as part of clinical care, usually before randomization. Where possible, a second research computed tomography or magnetic resonance imaging was performed at day 7+1 (end of treatment). Uncompressed DICOM, JPEG, PNG, or GIF image files were sent to the coordinating center, either uploaded via a secure website or on a compact disc. Images sent on film were digitized using a VICOM digitizer. Scans were assessed centrally using validated scales by expert neuroradiologists or trained neurologists (A.A., L.A.C., A.C., J.L.B., R.A.D., P.K., and J.M.W.) for the presence of hemorrhage, its location in the brain, the presence and amount of mass effect, the presence of blood in the subarachnoid space or ventricles, and underlying changes in the brain, including cerebral atrophy,[16] leukoaraiosis,[16] and the presence of old lesions.

Hematoma 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 hematoma/4π×area),[20] density index (SD/mean attenuation),[21] and the 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 K.K. 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 randomization. Secondary outcomes studied at day 90 included activities of daily living (Barthel Index[24]), cognition (modified telephone Mini-Mental State Examination[25]), Telephone Interview for Cognition Scale,[26] and health-related quality of life (European Quality of Life-5 dimensions-3 level,[27] from which health utility status was calculated,[28] and mood [short Zung Depression Scale score[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 >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 centers, 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 randomized within 6 hours of onset. Data are shown as number (%), median [interquartile range], or mean (SD). Patients who died were allocated an extreme score: −5: Barthel Index; −1: EQ-Visual Analogue Scale, SSS, telephone Mini-Mental State Examination, Telephone Interview for Cognition Scale, verbal fluency; 0: health utility status (derived from European Quality of Life-5 dimensions-3 level); 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 randomization, hematoma volume, and treatment assignment (GTN versus no GTN). Odds ratio, hazard ratio, or mean difference, with 95% confidence intervals, is 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 2 groups. The average age was 67 years; 66% of patients were men; 54% were enrolled from the United Kingdom; mean time from onset to recruitment was 25 hours; and mean stroke severity was 30.5 (SD, 12.4) on the SSS, equivalent to National Institute of Health Stroke Scale (NIHSS) score 12.6 (5.3).[31]

Table 1. Baseline Clinical and Neuroimaging Characteristics of All Patients With Intracerebral Hemorrhage and Those Randomized Within 6 Hours

	All	GTN	No GTN	All ≤6 h	GTN	No GTN	2p
Clinical characteristics							
No. of patients, n	629	310	319	61	29	32	…
Age, y	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, men (%)	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 (%)							
United Kingdom	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 randomization, h	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 h (%)	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
Ischemic 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, mm Hg							
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 h	414 (70.5)	220 (74.3)	194 (66.7)	53 (93.0)	27 (96.4)	26 (89.7)	0.78
>12 h	173 (29.5)	76 (25.7)	97 (33.3)	4 (7.0)	1 (3.6)	3 (10.3)	0.50
Adjudicated findings							
Hematoma 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, cm^3	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, cm^3	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

(*Continued*)

Table 1. Continued

	All	GTN	No GTN	All ≤6 h	GTN	No GTN	2p
Without IVH (n=436, 74.3%)							
Volume, ABC/2, cm^3	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

Data are number (%), median [interquartile range], or mean (SD). Comparison of patients randomized within 6 hours vs those randomized later by Fisher exact test, Mann–Whitney *U* test, or *t* test. Shape index was calculated as perimeter of hematoma/4π×surface area.[20] Density index was determined as SD/mean Hounsfield attenuation unit. CT indicates computed tomography; GTN, glyceryl trinitrate; IVH, intraventricular hemorrhage; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; SSS, Scandinavian Stroke Scale; and TACS, total anterior circulation syndrome.

*Lobar: border zone regions, cerebellar or brain stem, anterior cerebral artery, posterior cerebral artery territory, and MCA territory, excluding striatocapsular regions.

†Deep: lacunar, MCA territory, including striatocapsular regions.

A majority (71%) of patients had their baseline scans performed within 12 hours of onset (Table 1). Eighty-seven percent of hemorrhages were deep-seated in the lacunar and striatocapsular brain regions, most hematomas (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 hematoma volume was 13.3 cm^3, and 153 (26%) patients had an intraventricular hemorrhage. Additional information on baseline neuroimaging is given in Table I in the online-only Data Supplement.

Blood Pressure

Mean BP at baseline was 172.1/93.4 mm Hg 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 mm Hg (*P*=0.02/0.05, respectively); BP did not differ thereafter (Figure I in the online-only Data Supplement).

Clinical Outcomes

At day 90, the median mRS was 3 (interquartile range, 2) in both the GTN and no GTN groups and did not differ in an adjusted analysis (common odds ratio, 1.04; 95% confidence

Table 2. Secondary Outcomes at Day 7 and Day 90 for All Patients With Intracerebral Hemorrhage and Those Randomized Within 6 Hours

Outcome	n	GTN	No GTN	OR/MD (95% CI)	2 *P* Value	≤6 h	GTN	No GTN	OR/MD (95% CI)	2 *P* Value
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 to 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 to 1.69)	0.80	60	33.4 (16.4)	27.1 (19.6)	7.0 (1.0 to 13.1)	0.033
Recurrence (%)	626	8 (2.6)	4 (1.3)	2.43 (0.63 to 9.29)	0.19	60	0	1 (3.1)	…	1.00
Hospital events	623	308	315	…	…	59	29	30	…	…
Died in hospital (%)	623	28 (9.0)	32 (10.2)	0.92 (0.48 to 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 to 1.22)	0.37	59	14 (48.3)	14 (46.7)	1.20 (0.32 to 4.43)	0.79
Day 90	623	309	316	…		61	29	32	…	…
Death (%)	625	42 (13.6)	47 (14.9)	0.91 (0.55 to 1.55)	0.76	61	2 (6.9)	12 (37.5)	*	0.006
mRS [/6]	625	3 [2]	3 [2]	1.04 (0.78 to 1.38)	0.81	61	3 [2]	4 [4]	0.19 (0.06 to 0.59)	0.004
Barthel Index	622	62.3 (38.1)	61.4 (39.7)	1.26 (–3.65 to 6.17)	0.62	61	66.9 (36.4)	46.9 (45.7)	20.71 (6.34 to 35.07)	0.005
t-MMSE	369	10 (7.2)	10.1 (7.4)	0.04 (–1.20 to 1.28)	0.95	38	11.9 (6.4)	6.5 (8.3)	3.38 (–0.29 to 7.10)	0.008
TICS-M	370	11.9 (9.3)	12.7 (9.3)	–0.64 (–2.20 to 0.93)	0.43	39	16.6 (9.1)	7.1 (9.3)	7.17 (2.20 to 12.12)	0.005
Animal naming (/∞)	376	8.2 (7.8)	7.9 (7.4)	0.28 (–1.09 to 1.65)	0.69	39	12.8 (8.0)	4.8 (7.3)	7.92 (2.93 to 12.92)	<0.001
ZDS (/100)	516	60.1 (24.2)	59.6 (24.3)	0.62 (–3.12 to 4.43)	0.73	50	54.2 (20.6)	71.8 (28.6)	–17.58 (–32.25 to –3.01)	<0.001
HUS (/1)	621	0.45 (0.31)	0.46 (0.32)	–0.01 (–0.05 to 0.03)	0.60	61	0.53 (0.3)	0.53 (0.32)	0.19 (0.06 to 0.32)	0.003
EQ-VAS (/100)	543	54.6 (31.3)	55.1 (31.5)	–0.44 (–5.16 to 4.27)	0.85	57	60.9 (26.7)	40.4 (38.1)	21.28 (6.31 to 36.25)	0.005
Dead or institution (%)	616	97 (31.4)	92 (29.1)	1.09 (0.72 to 1.67)	0.68	61	13 (44.8)	14 (43.8)	0.51 (0.12 to 2.18)	0.36

Data are number of patients (%), mean (SD) or median [interquartile range] with 95% confidence intervals. Comparison by logistic regression, ordinal regression, or multiple regression with adjustment for age, sex, premorbid mRS, history of previous stroke, history of diabetes mellitus, severity, total anterior circulation syndrome, volume of intracerebral hemorrhage, systolic blood pressure, feeding status, time to randomization and allocation to continue or stop prestroke antihypertensive drugs. EQ-VAS indicates EQ-Visual Analogue Scale; GTN, glyceryl trinitrate; HUS, health utility status; mRS, modified Rankin Scale; SSS, Scandinavian Stroke Scale; t-MMSE, modified telephone Mini-Mental State Examination; TICS-M, modified Telephone Interview for Cognitive Status; and ZDS, Zung Depression Scale.

*Fisher exact test.

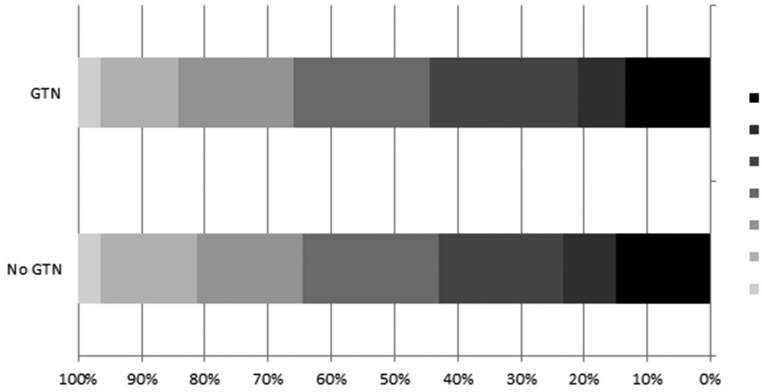

Figure 1. Distribution of modified Rankin Scale scores for all 625 patients with intracerebral hemorrhage at day 90: glyceryl trinitrate (GTN) versus no GTN. Comparison by ordinal logistic regression adjusted for age, sex, premorbid mRS, history of previous stroke, history of diabetes mellitus, total anterior circulation syndrome, systolic blood pressure, feeding status, time to randomization, and allocation to continue or stop prestroke antihypertensive drugs. Adjusted common odds ratio, 1.04 (95% confidence interval, 0.78–1.38; *P*=0.81).

interval, 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 randomization and

Table 3. Relationships Between Baseline Imaging Characteristics and Functional Outcome (modified Rankin Scale) at Day 90

Hematoma Characteristics	Univariate Analyses OR/MD (95% CI)	2 *P* Value	Covariate Adjusted OR/MD (95% CI)	2 *P* Value
Hematoma 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 hemorrhage	2.22 (1.50–3.28)	<0.0001	1.47 (0.97–2.21)	0.07
Intraventricular hemorrhage	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 hemorrhage	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, cm^3	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
Hemorrhage shape (/5)	1.36 (1.23–1.51)	<0.0001	1.28 (1.15–1.42)	<0.0001
Hemorrhage density (/5)	1.42 (1.27–1.60)	<0.0001	1.27 (1.13–1.42)	<0.0001
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
Hemorrhages with IVH				
Volume ABC/2, cm^3	1.01 (0.99–1.02)	0.19	1.00 (0.97–1.03)	0.94
IVH volume, cm^3	1.02 (0.98–1.06)	0.40	1.01 (0.97–1.06)	0.56
Hemorrhage shape (/5)	1.31 (1.03–1.67)	0.026	1.42 (1.11–1.82)	<0.0001
Hemorrhage 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

Results are OR or MD with 95% CI 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. CI indicates confidence interval; IVH, intraventricular hemorrhage; MD, mean difference; and OR, odds ratio.

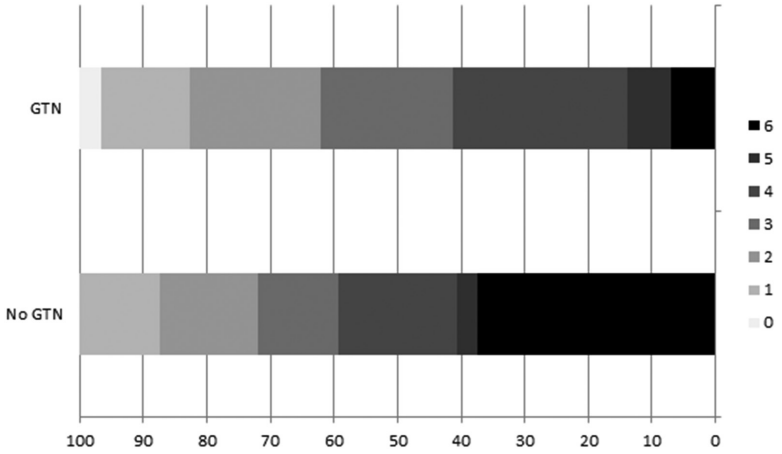

Figure 2. Distribution of modified Rankin Scale scores for patients randomized within 6 hours at day 90: glyceryl trinitrate (GTN, n=29) versus no GTN (n=32). Comparison by ordinal logistic regression adjusted for age, sex, premorbid mRS, history of previous stroke, history of diabetes mellitus, total anterior circulation syndrome, systolic blood pressure, feeding status, time to randomization, and allocation to continue versus stop prestroke antihypertensive drugs. Adjusted common odds ratio, 0.19 (95% confidence interval, 0.06–0.59; *P*=0.004).

stroke subtype (Figures II and III in the online-only Data Supplement).

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% confidence interval, 0.67–1.56, *P*=0.92; Figure IV in the online-only Data Supplement). There were no significant differences between the 2 groups in any of the secondary outcomes studied at day 7 or day 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% versus 21.9%; *P*=0.50; Table II in the online-only Data Supplement).

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 covariate-adjusted analyses comprised the presence of intraventricular hemorrhage or atrophy, irregular hematoma shape, and heterogeneous density.

Patients Randomized Within 6 Hours

Of the 629 patients with ICH, 61 (9.7%) participants were randomized 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 hemorrhage volume (mean, 16.9 cm^3), and were more likely to have intraventricular hemorrhage.

Patients randomized 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 randomized 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 randomized to GTN versus no GTN (adjusted hazard ratio, 0.19; 95% confidence interval, 0.03–1.01; *P*=0.051).

Effect of GTN on Hemorrhage Measures at Day 7

One hundred and eighty-one patients had repeat brain imaging at 1 week for an assessment of the effect on hemorrhage 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 hematoma 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 when compared with no GTN. This result mirrors that across the main study and is in spite of GTN reducing BP by 7.5/4.2 mm Hg. Furthermore, 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 2 treatment groups suggests that treatment with GTN is safe. In a prespecified analysis of the effect of treatment in patients randomized 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 several explanations. First, patients could be randomized ≤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 randomized within 6 hours of ICH onset into ENOS seemed to benefit with less dependency, disability, impairment and mood disturbance, and better cognition and quality of life. Very early BP lowering might help limit hematoma expansion.[32,33] Second, the degree by which BP was lowered may have been too small; INTERACT-2 achieved a reduction of 14 mm Hg by 6 hours and showed a near-significant effect on functional outcome.[5] Finally, 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 randomized into the large SCAST,[6] where oral candesartan was associated

Table 4. Effect of Treatment on Neuroimaging Measures at Day 7 in 181 Patients With a Baseline Scan Before Randomization, for All Patients With Intracerebral Hemorrhage

	All			
Scan Variables	GTN	No GTN	Adjusted OR/MD (95% CI)	2 *P* Value
Hematoma location	93	88	…	…
Lobar (%)	10 (10.8)	11 (12.5)	1.24 (0.49 to 3.15)	0.66
Deep (%)	83 (89.2)	77 (42.5)	0.63 (0.10 to 3.85)	0.61
Intraventricular hemorrhage (%)	25 (26.9)	19 (21.6)	0.85 (0.43 to 1.70)	0.65
Subarachnoid hemorrhage (%)	7 (7.5)	11 (12.5)	0.50 (0.17 to 1.49)	0.21
Mass effect (%)	79 (84.9)	81 (92.0)	1.04 (0.72 to 1.50)	0.84
Brain tissue reduction (%)	53 (57.0)	59 (67.0)	0.51 (0.24 to 1. 10)	0.09
Cortical atrophy (%)	44 (47.3)	42 (47.7)	1.26 (0.47 to 3.36)	0.64
Central atrophy (%)	48 (51.6)	58 (65.9)	0.92 (0.60 to 2.10)	0.73
Leukoaraiosis (%)	64 (68.8)	63 (71.6)	0.83 (0.37 to 1.87)	0.66
Previous stroke lesion (%)	41 (44.1)	51 (60.0)	0.57 (0.28 to 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, cm^3	15.4 (16.0)	19.2 (21.4)	−4.30 (−8.78 to 0.23)	0.06
Largest measured diameter	3.6 (1.3)	3.8 (1.6)	−0.04 (−0.33 to 0.25)	0.81
Shape index	1.7 (0.8)	1.7 (1.0)	−0.04 (−0.31 to 0.24)	0.80
Shape [/5]	2 [2–3]	2 [1–3]	0.14 (−0.19 to 0.47)	0.41
Density index	0.4 (0.7)	0.3 (0.5)	0.10 (-0.07 to 0.28)	0.27
Density [/5]	2 [1–3]	2 [1–3]	0.12 (−0.18 to 0.43)	0.43
No IVH (n=137)				
Volume ABC/2, cm^3	14.7 (15.3)	18.4 (18.4)	−4.52 (−9.05 to 0.01)	0.05
Shape index	1.5 (0.6)	1.7 (1.0)	−0.12 (0.42 to 0.17)	0.42
Shape [/5]	2 [1–3]	2 [2–3]	0.04 (−0.31 to 0.39)	0.82
Density index	0.4 (0.9)	0.3 (0.7)	0.15 (−0.11 to 0.41)	0.26
Density [/5]	2 [1–3]	2 [1–3]	0.34 (−0.03 to 0.71)	0.07
With IVH (n=44)				
Volume ABC/2, cm^3	17.1 (17.9)	18.4 (17.4)	−0.64 (−8.53 to 7.24)	0.87
IVH volume, cm^3	3.0 (6.0)	3.7 (5.9)	0.52 (−4.96 to 6.01)	0.85
Shape index	2.0 (1.0)	2.1 (1.2)	−0.12 (−0.79 to 0.55)	0.73
Shape [/5]	4 [3–5]	4 [3–5]	1.00 (0.50 to 1.99)	0.99
Density index	0.3 (0.1)	0.3 (0.1)	−0.01 (−0.06 to 0.04)	0.66
Density [/5]	2 [1–3]	2 [1–3]	0.00 (−0.64 to 0.63)	1.00
Graeb score	2.9 (1.8)	2.1 (1.3)	0.94 (−0.25 to 2.12)	0.12
Modified Graeb score	3.4 (2.7)	2.5 (2.2)	1.23 (−0.59 to 3.05)	0.18

Data are number (%), median [interquartile range], or mean (SD), and odds ratio or mean difference with 95% CIs. Comparison by logistic regression, ordinal regression, or multiple regression with adjustment for baseline value. CI indicates confidence interval; GTN, glyceryl trinitrate; IVH, intraventricular hemorrhage; MD, mean difference; and OR, odds ratio.

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 mm Hg.

The reduction in ICH volume in the GTN group (4 cm^3) was similar to the effect observed in trials of recombinant activated clotting factor VII, although the agent was tested in earlier time windows.[34,35] Mechanisms by which nitric oxide donors might reduce hematoma volume and improve functional outcome if given early include lowering BP, neuroprotection, and improving collateral blood flow. The latter 2 effects have been seen in experimental models of brain ischemia[36,37] and may be of relevance after ICH.

This subgroup analysis of ENOS has several strengths, including recruitment of patients with ICH from multiple ethnic groups across 5 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 prespecified.[12] However, exclusion of patients with low or normal BP (systolic BP <140 mm Hg) or very high (>220 mm Hg), those with reduced consciousness (GCS score <8), and those without motor signs may have limited the external validity of the findings and especially the number of patients with large hematoma.

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 seems 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 randomized within 6 hours of ICH onset and recent guidelines[38,39] support ongoing or planned trials of lowering BP in the ultra-acute and hyperacute periods after stroke, including the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) Trial of intravenous nicardipine[40] and RIGHT-2 of GTN administered in the prehospital phase of stroke (ISTRCTN26986053).

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References

1. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2014;85:660–667. doi: 10.1136/jnnp-2013-306476.
2. Willmot M, Leonardi-Bee J, Bath PM. High blood pressure in acute stroke and subsequent outcome: a systematic review. *Hypertension*. 2004;43:18–24. doi: 10.1161/01.HYP.0000105052.65787.35.
3. Terayama Y, Tanahashi N, Fukuuchi Y, Gotoh F. Prognostic value of admission blood pressure in patients with intracerebral hemorrhage. Keio Cooperative Stroke Study. *Stroke*. 1997;28:1185–1188.
4. Qureshi AI, Mohammad YM, Yahia AM, Suarez JI, Siddiqui AM, Kirmani JF, et al. A prospective multicenter study to evaluate the feasibility and safety of aggressive antihypertensive treatment in patients with acute intracerebral hemorrhage. *J Intensive Care Med*. 2005;20:34–42. doi: 10.1177/0885066604271619.
5. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al; INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368:2355–2365. doi: 10.1056/NEJMoa1214609.
6. Jusufovic M, Sandset EC, Bath PM, Berge E; Scandinavian Candesartan Acute Stroke Trial Study Group. Blood pressure-lowering treatment with candesartan in patients with acute hemorrhagic stroke. *Stroke*. 2014;45:3440–3442. doi: 10.1161/STROKEAHA.114.006433.
7. Bath PM, Pathansali R, Iddenden R, Bath FJ. The effect of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure and platelet function in acute stroke. *Cerebrovasc Dis*. 2001;11:265–272. doi: 10.1159/000047649.
8. Rashid P, Weaver C, Leonardi-Bee J, Bath F, Fletcher S, Bath P. The effects of transdermal glyceryl trinitrate, a nitric oxide donor, on blood pressure, cerebral and cardiac hemodynamics, and plasma nitric oxide levels in acute stroke. *J Stroke Cerebrovasc Dis*. 2003;12:143–151. doi: 10.1016/S1052-3057(03)00037-5.
9. Willmot M, Ghadami A, Whysall B, Clarke W, Wardlaw J, Bath PM. Transdermal glyceryl trinitrate lowers blood pressure and maintains cerebral blood flow in recent stroke. *Hypertension*. 2006;47:1209–1215. doi: 10.1161/01.HYP.0000223024.02939.1e.
10. Ankolekar S, Fuller M, Cross I, Renton C, Cox P, Sprigg N, et al. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: the rapid intervention with glyceryl trinitrate in Hypertensive Stroke Trial (RIGHT, ISRCTN66434824). *Stroke*. 2013;44:3120–3128. doi: 10.1161/STROKEAHA.113.001301.
11. Bath PMW, Woodhouse L, Scutt P, Krishnan K, Wardlaw JM, Bereczki D, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet*. 2015;385:617–628.
12. Bath PM, Houlton A, Woodhouse L, Sprigg N, Wardlaw J, Pocock S; ENOS Trialists. Statistical analysis plan for the 'Efficacy of Nitric Oxide in Stroke' (ENOS) trial. *Int J Stroke*. 2014;9:372–374. doi: 10.1111/ijs.12235.
13. The ENOS Trial Investigators. Glyceryltrinitrate vs. control, and continuing vs.stopping temporarily prior antihypertensive therapy in acute stroke: rationale and design of the efficacy of nitric oxide (ENOS) trial (ISRCTN99414122). *Int J Stroke*. 2006;1:245–249.
14. ENOS Investigators. Baseline characteristics of the 4011 patients recruited into the "Efficacy of Nitric Oxide in Stroke" (ENOS) trial. *Int J Stroke*. 2014;9:711–720.
15. O'Brien E, Mee F, Atkins N, Thomas M. Evaluation of three devices for self-measurement of blood pressure according to the revised British Hypertension Society Protocol: the Omron HEM-705CP, Philips HP5332, and Nissei DS-175. *Blood Press Monit*. 1996;1:55–61.
16. Wardlaw JM, Sellar R. A simple practical classification of cerebral infarcts on CT and its interobserver reliability. *AJNR Am J Neuroradiol*. 1994;15:1933–1939.
17. Kwak R, Kadoya S, Suzuki T. Factors affecting the prognosis in thalamic hemorrhage. *Stroke*. 1983;14:493–500.
18. Rosset A, Spadola L, Ratib O. OsiriX: an open-source software for navigating in multidimensional DICOM images. *J Digit Imaging*. 2004;17:205–216. doi: 10.1007/s10278-004-1014-6.
19. Barras CD, Tress BM, Christensen S, MacGregor L, Collins M, Desmond PM, et al; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Density and shape as CT predictors of intracerebral hemorrhage growth. *Stroke*. 2009;40:1325–1331. doi: 10.1161/STROKEAHA.108.536888.
20. Pabst W, Gregerova E. Characterisation of particle and particle systems. *ICT*. 2007:1–123.
21. Barras CD, Tress BM, Christensen S, Collins M, Desmond PM, Skolnick BE, et al; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Quantitative CT densitometry for predicting intracerebral hemorrhage growth. *AJNR Am J Neuroradiol*. 2013;34:1139–1144. doi: 10.3174/ajnr.A3375.
22. Graeb DA, Robertson WD, Lapointe JS, Nugent RA, Harrison PB. Computed tomographic diagnosis of intraventricular hemorrhage. Etiology and prognosis. *Radiology*. 1982;143:91–96. doi: 10.1148/radiology.143.1.6977795.
23. Morgan TC, Dawson J, Spengler D, Lees KR, Aldrich C, Mishra NK, et al; CLEAR and VISTA Investigators. The Modified Graeb Score: an enhanced tool for intraventricular hemorrhage measurement and prediction of functional outcome. *Stroke*. 2013;44:635–641. doi: 10.1161/STROKEAHA.112.670653.
24. Sulter G, Steen C, De Keyser J. Use of the Barthel Index and modified Rankin Scale in acute stroke trials. *Stroke*. 1999;30:1538–1541.
25. Metitieri T, Geroldi C, Pezzini A, Frisoni GB, Bianchetti A, Trabucchi M. The Itel-MMSE: an Italian telephone version of the Mini-Mental State Examination. *Int J Geriatr Psychiatry*. 2001;16:166–167.
26. Desmond DW, Tatemichi TK, Hanzawa L. The Telephone Interview for Cognitive Status (TICS): reliability and validity in a stroke sample. *Int J Geriatr Psychiatry*. 1994;9:803–807.

27. Whynes DK, Sprigg N, Selby J, Berge E, Bath PM; ENOS Investigators. Testing for differential item functioning within the EQ-5D. *Med Decis Making*. 2013;33:252–260. doi: 10.1177/0272989X12465016.
28. Sprigg N, Selby J, Fox L, Berge E, Whynes D, Bath PM; Efficacy of Nitric Oxide in Stroke Investigators. Very low quality of life after acute stroke: data from the Efficacy of Nitric Oxide in Stroke trial. *Stroke*. 2013;44:3458–3462. doi: 10.1161/STROKEAHA.113.002201.
29. Zung WW. A self-rating depression scale. *Arch Gen Psychiatry*. 1965;12:63–70.
30. Ankolekar S, Renton C, Sare G, Ellender S, Sprigg N, Wardlaw JM, et al; ENOS Trial Investigators. Relationship between poststroke cognition, baseline factors, and functional outcome: data from "efficacy of nitric oxide in stroke" trial. *J Stroke Cerebrovasc Dis*. 2014;23:1821–1829. doi: 10.1016/j.jstrokecerebrovasdis.2014.04.022.
31. Gray LJ, Ali M, Lyden PD, Bath PM; Virtual International Stroke Trials Archive Collaboration. Interconversion of the National Institutes of Health Stroke Scale and Scandinavian Stroke Scale in acute stroke. *J Stroke Cerebrovasc Dis*. 2009;18:466–468. doi: 10.1016/j.jstrokecerebrovasdis.2009.02.003.
32. Anderson CS, Huang Y, Wang JG, Arima H, Neal B, Peng B, et al; INTERACT Investigators. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. *Lancet Neurol*. 2008;7:391–399. doi: 10.1016/S1474-4422(08)70069-3.
33. Qureshi AI, Palesch YY, Martin R, Novitzke J, Cruz-Flores S, Ehtisham A, et al; Antihypertensive Treatment of Acute Cerebral Hemorrhage Study Investigators. Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage: results from the antihypertensive treatment of acute cerebral hemorrhage study. *Arch Neurol*. 2010;67:570–576. doi: 10.1001/archneurol.2010.61.
34. Mayer SA, Brun NC, Broderick J, Davis S, Diringer MN, Skolnick BE, et al; Europe/AustralAsia NovoSeven ICH Trial Investigators. Safety and feasibility of recombinant factor VIIa for acute intracerebral hemorrhage. *Stroke*. 2005;36:74–79. doi: 10.1161/01.STR.0000149628.80251.b8.
35. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al; FAST Trial Investigators. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2008;358:2127–2137. doi: 10.1056/NEJMoa0707534.
36. Willmot M, Gray L, Gibson C, Murphy S, Bath PM. A systematic review of nitric oxide donors and L-arginine in experimental stroke; effects on infarct size and cerebral blood flow. *Nitric Oxide*. 2005;12:141–149. doi: 10.1016/j.niox.2005.01.003.
37. Morikawa E, Rosenblatt S, Moskowitz MA. L-arginine dilates rat pial arterioles by nitric oxide-dependent mechanisms and increases blood flow during focal cerebral ischaemia. *Br J Pharmacol*. 1992;107:905–907.
38. Steiner T, Al-Shahi Salman R, Beer R, Christensen H, Cordonnier C, Csiba L, et al; European Stroke Organisation. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. *Int J Stroke*. 2014;9:840–855. doi: 10.1111/ijs.12309.
39. Hemphill JC III, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2015;46:2032–2060. doi: 10.1161/STR.0000000000000069.
40. Qureshi AI, Palesch YY. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: design, methods, and rationale. *Neurocrit Care*. 2011;15:559–576. doi: 10.1007/s12028-011-9538-3.

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

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SUPPLEMENTAL MATERIAL

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

Supplementary Tables:

I Additional information on baseline scan adjudication and measurements.

II Serious adverse events.

Supplementary Figures:

I. Blood pressure profile by treatment group.

II. Clinical subgroups.

III. Neuroimaging subgroups.

IV. Survival curves for all patients.

Supplementary Table I. Additional information on baseline neuroimaging data for all patients with intracerebral haemorrhage and those randomised within 6 hours. Data are number (%), median [interquartile range], or mean (standard deviation).

Neuroimaging	All	GTN	No GTN	<6 hours	GTN	No GTN
Number of patients (N)	629	310	319	61	29	32
Participants with a scan available	587 (93.3)	296 (95.5)	291 (91.2)	57 (93.4)	28 (96.6)	29 (90.6)
Adjudicated findings						
Haematoma location (%)						
Lacune	155 (26.4)	83 (28.0)	72 (24.7)	13 (22.8)	6 (21.4)	7 (24.1)
Borderzone	16 (2.7)	6 (2.0)	10 (3.4)	1 (1.8)	1 (3.6)	0 (0)
Cerebellum and/or brainstem	17 (2.9)	9 (3.0)	8 (2.7)	2 (3.5)	1 (3.6)	1 (3.4)
MCA territory	372 (63.4)	183 (61.8)	189 (64.9)	38 (66.7)	19 (67.9)	19 (65.5)
ACA or PCA territory	27 (4.6)	15 (5.1)	12 (4.1)	3 (5.3)	1 (3.6)	2 (6.9)
Longest diameter (cm)						
<3	235 (40.4)	119 (40.8)	116 (40.1)	24 (42.1)	12 (42.9)	12 (41.4)
3-5	242 (41.7)	120 (41.1)	122 (42.2)	19 (33.3)	10 (35.7)	9 (31.0)
5-8	93 (16.0)	45 (15.4)	48 (16.6)	12 (21.1)	4 (14.3)	8 (27.6)
>8	11 (1.9)	8 (2.7)	3 (1.0)	2 (3.5)	2 (7.1)	0 (0)

Sub-arachnoid haemorrhage (%)	94 (16.0)	47 (15.9)	47 (16.2)	10 (17.5)	4 (14.3)	6 (20.7)
Subdural haematoma (%)	4 (0.7)	2 (0.7)	2 (0.7)	1 (1.8)	1 (3.6)	0 (0)
Remote ICH (%)	4 (0.7)	3 (1.0)	1 (0.3)	0 (0)	0 (0)	0 (0)
Measured CT scan findings						
Diameter, max (cm)	3.4 (1.4)	3.4 (1.4)	3.5 (1.4)	3.6 (1.4)	3.5 (1.4)	3.6 (1.5)
With IVH (n=151, 25.7%)						
Shape (/5)[1]	5.0 [2.0]	5.0 [2.0]	5.0 [1.0]	5.0 [0.5]	5.0 [1.0]	5.0 [0.0]
Density (/5)[1]	3.0 [2.0]	3.0 [2.0]	3.0 [2.0]	3.0 [3.0]	2.0 [2.0]	4.0 [2.0]
Modified Graeb score (/32)[2]	3.0 [4.5]	3.0 [4.0]	3.0 [5.0]	6.5 [7.5]	4.0 [5.0]	7.0 [6.0]
Without IVH (n=436, 74.3%)						
Shape (/5)[1]	3.0 [2.0]	3.0 [2.0]	3.0 [2.0]	2.0 [2.5]	2.0 [2.0]	3.0 [3.0]
Density (/5)[1]	2.0 [1.0]	2.0 [1.0]	2.0 [1.0]	2.0 [1.0]	2.0 [1.0]	2.0 [2.0]

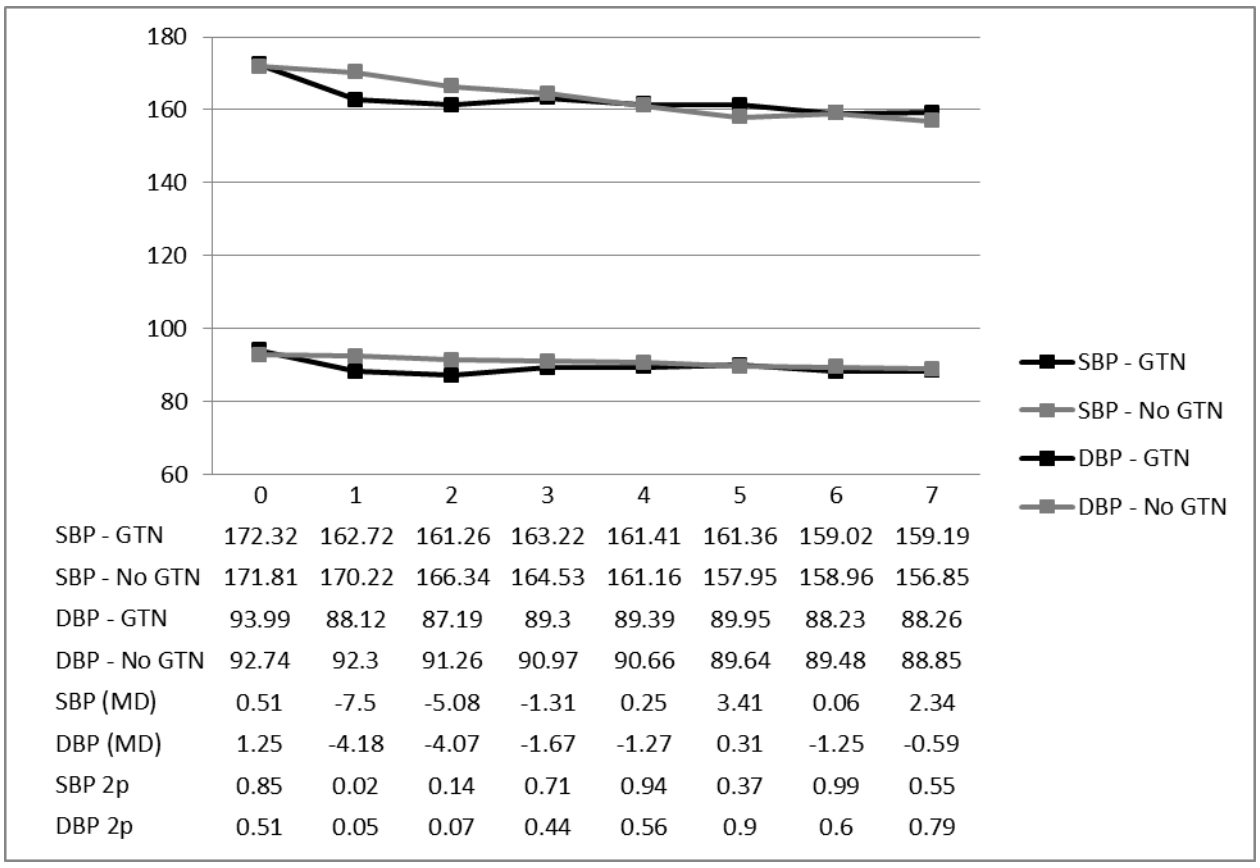
ACA: anterior cerebral artery; ICH: intracerebral haemorrhage; MCA: middle cerebral artery; PCA: posterior cerebral artery.

Intracerebral haemorrhage shape and density were determined using a 5-point ordered categorical scale.

Supplementary Table II. Serious adverse events at day 90 for all patients with intracerebral haemorrhage at day 90 and those randomised within 6 hours. Data are number of patients (%) and mean (standard deviation). NA denotes not applicable.

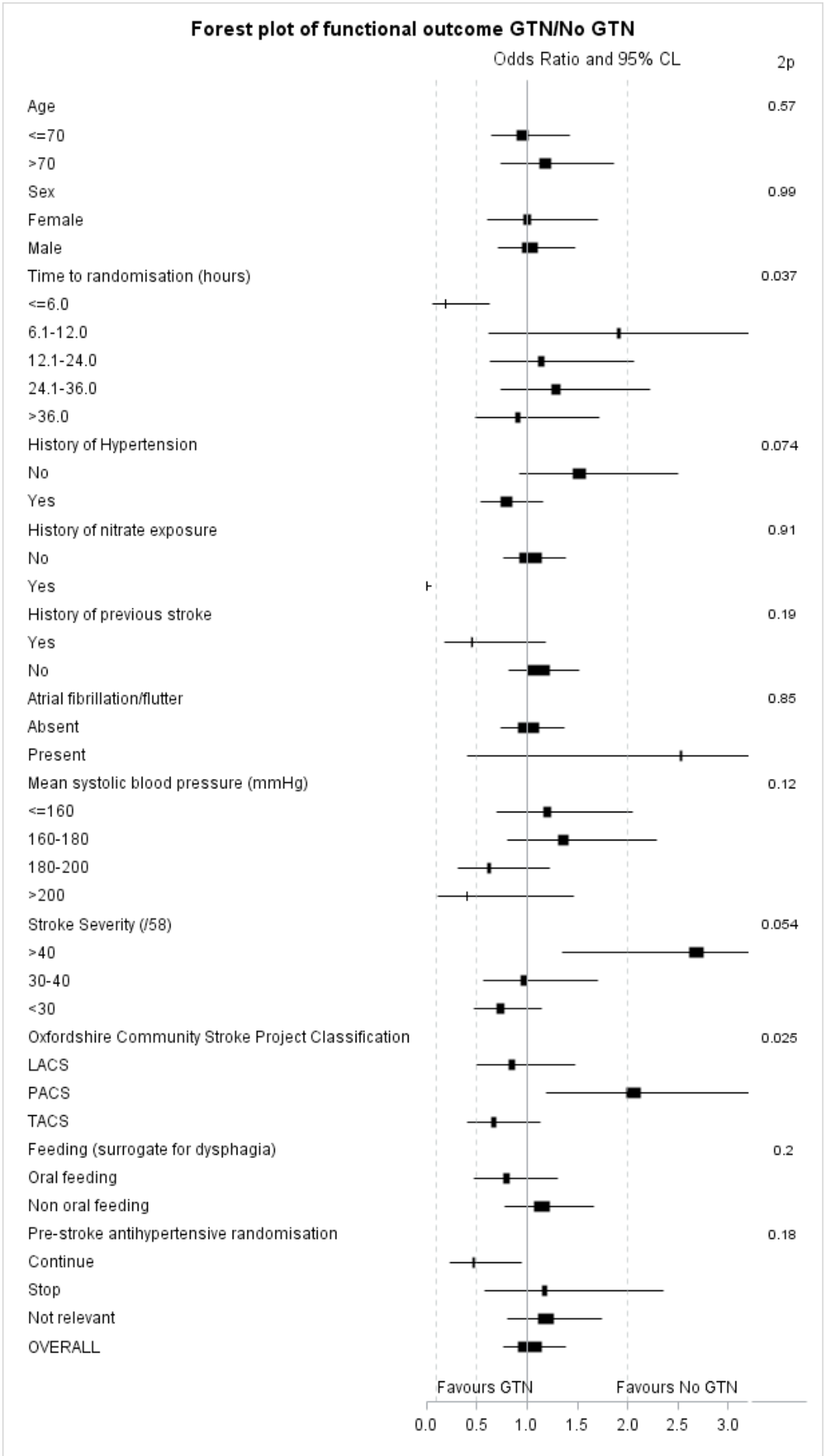
	All			<6 hours		
	GTN	No GTN	2p	GTN	No GTN	2p
Complication of initial stroke	13 (4.2)	9 (2.8)	0.35	0	2 (6.3)	0.50
Extension of initial stroke	13 (4.2)	4 (1.3)	0.027	1 (3.4)	3 (9.4)	0.61
Recurrent stroke	7 (2.3)	7 (2.2)	0.96	0	0	NA
Myocardial infarction	1 (0.3)	2 (0.6)	1.00	0	2 (6.3)	0.49
Other cardiovascular cause	10 (3.2)	20 (6.3)	0.07	1 (3.4)	3 (9.4)	0.61
Pulmonary embolism	4 (1.3)	4 (1.3)	1.00	0	0	NA
Pneumonia	13 (4.2)	25 (7.8)	0.06	1 (3.4)	2 (6.3)	1.00
Sudden cardiac death	1 (0.3)	1 (0.3)	1.00	0	1 (3.1)	1.00
Other cause	4 (1.3)	4 (1.3)	1.00	2 (6.9)	1 (3.1)	1.00
Total SAEs	75 (24.2)	70 (21.9)	0.50	5 (17.2)	14 (43.8)	0.026

Supplementary Figure I. Blood pressure levels for patients with intracerebral haemorrhage during 7 days treatment for GTN versus no GTN group. Blood pressure was 172/93 mm Hg at baseline and was significantly lower in 310 patients allocated to GTN as compared to 319 patients randomised to no GTN: difference -7.5/-4.2 mm Hg. MD signifies mean difference in systolic and diastolic blood pressure between the two treatment groups.

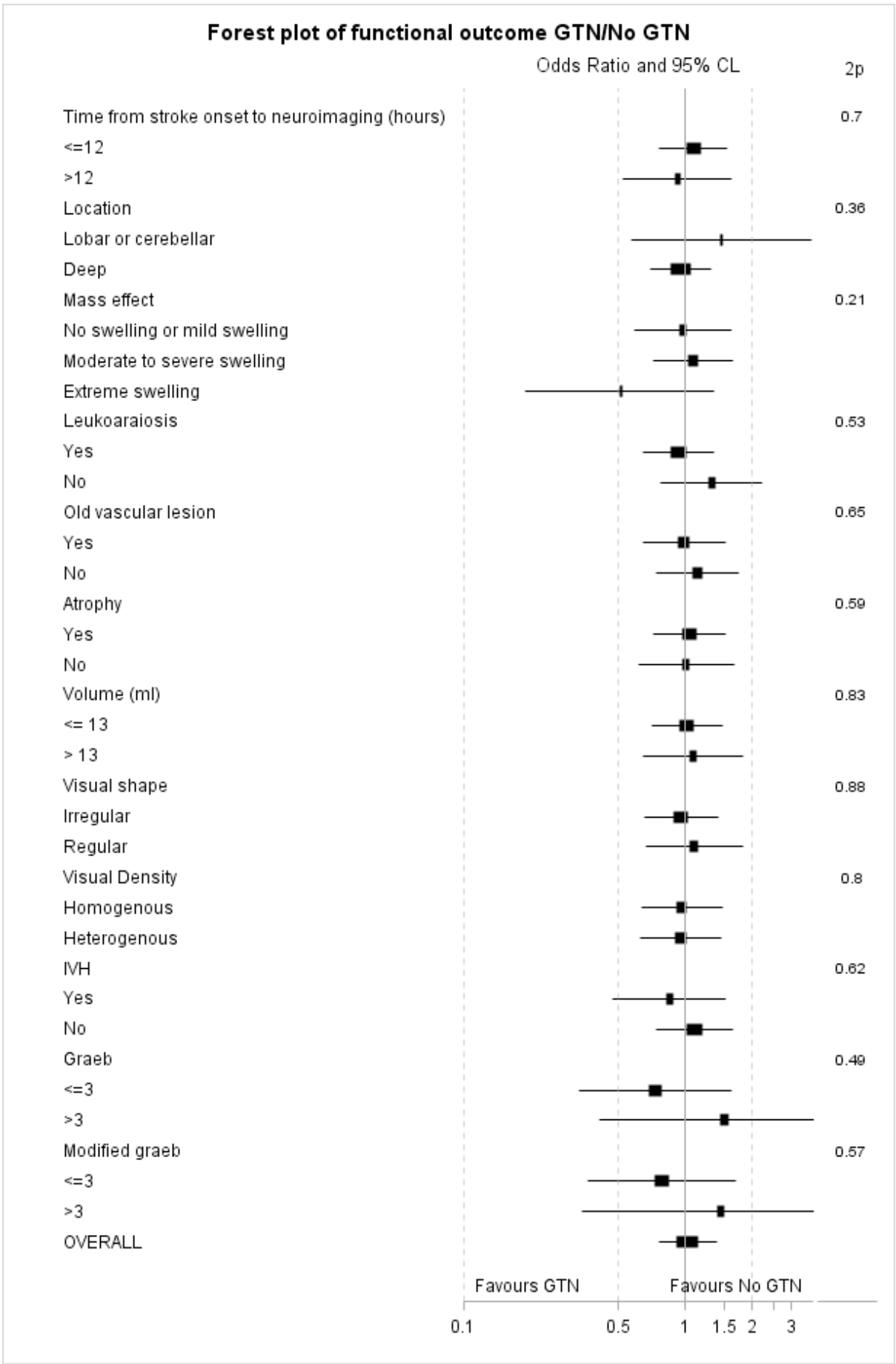


	0	1	2	3	4	5	6	7
SBP - GTN	172.32	162.72	161.26	163.22	161.41	161.36	159.02	159.19
SBP - No GTN	171.81	170.22	166.34	164.53	161.16	157.95	158.96	156.85
DBP - GTN	93.99	88.12	87.19	89.3	89.39	89.95	88.23	88.26
DBP - No GTN	92.74	92.3	91.26	90.97	90.66	89.64	89.48	88.85
SBP (MD)	0.51	-7.5	-5.08	-1.31	0.25	3.41	0.06	2.34
DBP (MD)	1.25	-4.18	-4.07	-1.67	-1.27	0.31	-1.25	-0.59
SBP 2p	0.85	0.02	0.14	0.71	0.94	0.37	0.99	0.55
DBP 2p	0.51	0.05	0.07	0.44	0.56	0.9	0.6	0.79

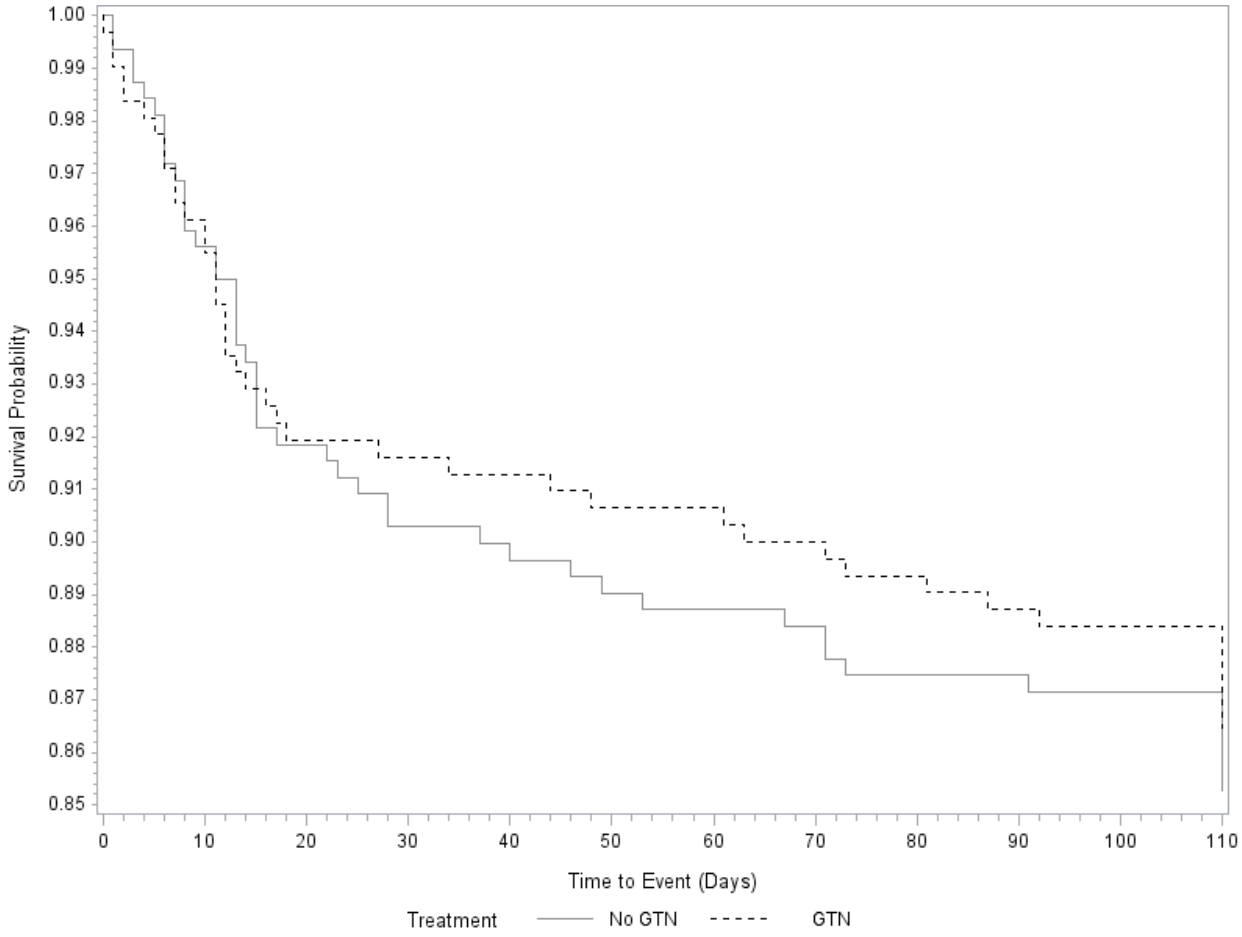
Supplementary Figure II. Effect of glyceryl trinitrate versus no glyceryl trinitrate on distribution of modified Rankin Scale in pre-specified clinical subgroups of patients with intracerebral haemorrhage at day 90. Analysis adjusted for age, sex, pre-morbid mRS, history of previous stroke, history of diabetes, severity, total anterior circulation syndrome, volume of intracerebral haemorrhage, systolic blood pressure, feeding status and time to randomisation. Black squares indicate point estimates (with the area of the square proportional to the number of events) and the width of the horizontal lines is the 95% confidence interval of the estimate. The rectangle at the bottom represents the point estimate as well as the 95% confidence intervals of the overall effect within categories.


Forest plot of functional outcome GTN/No GTN
Odds Ratio and 95% CL
2p
Age
0.57
<=70
>70
Sex
0.99
Female
Male
Time to randomisation (hours)
0.037
<=6.0
6.1-12.0
12.1-24.0
24.1-36.0
>36.0
History of Hypertension
0.074
No
Yes
History of nitrate exposure
0.91
No
Yes
History of previous stroke
0.19
Yes
No
Atrial fibrillation/flutter
0.85
Absent
Present
Mean systolic blood pressure (mmHg)
0.12
<=160
160-180
180-200
>200
Stroke Severity (/58)
0.054
>40
30-40
<30
Oxfordshire Community Stroke Project Classification
0.025
LACS
PACS
TACS
Feeding (surrogate for dysphagia)
0.2
Oral feeding
Non oral feeding
Pre-stroke antihypertensive randomisation
0.18
Continue
Stop
Not relevant
OVERALL
Favours GTN
Favours No GTN
0.0
0.5
1.0
1.5
2.0
2.5
3.0

Supplementary Figure III. Effect of glyceryl trinitrate versus no glyceryl trinitrate on the primary outcome of modified Rankin Scale in pre-specified neuroimaging subgroups at day 90. Analysis adjusted 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. Black squares indicate point estimates (with the area of the square proportional to the number of events) and the width of the horizontal lines is the 95% confidence interval of the estimate. The rectangle at the bottom represents the point estimate as well as the 95% confidence intervals of the overall effect within categories.


Forest plot of functional outcome GTN/No GTN
Odds Ratio and 95% CL
2p
Time from stroke onset to neuroimaging (hours)
0.7
<=12
>12
Location
0.36
Lobar or cerebellar
Deep
Mass effect
0.21
No swelling or mild swelling
Moderate to severe swelling
Extreme swelling
Leukoaraiosis
0.53
Yes
No
Old vascular lesion
0.65
Yes
No
Atrophy
0.59
Yes
No
Volume (ml)
0.83
<= 13
> 13
Visual shape
0.88
Irregular
Regular
Visual Density
0.8
Homogenous
Heterogenous
IVH
0.62
Yes
No
Graeb
0.49
<=3
>3
Modified graeb
0.57
<=3
>3
OVERALL
Favours GTN
Favours No GTN
0.1
0.5
1
1.5
2
3

Supplementary Figure IV. Effect of glyceryl trinitrate versus no glyceryl trinitrate on survival to day 90 in patients with intracerebral haemorrhage. Comparison by Cox proportional hazards 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 hazard ratio 1.02 (95% CI 0.67-1.56), p=0.92.



REFERENCES

1. Barras CD, Tress BM, Christensen S, MacGregor L, Collins M, Desmond PM, et al. Density and shape as ct predictors of intracerebral hemorrhage growth. Stroke. 2009;40:1325-1331
2. Morgan T, Dawson J, Spengler D, Lees K, Aldrich C, Mishra N, et al. The modified Graeb score an enhanced tool for intraventricular hemorrhage measurement and prediction of functional outcome. Stroke. 2013;44:635-641