Original Contribution

Effect of Hyperacute Administration (Within 6 Hours) of Transdermal Glyceryl Trinitrate, a Nitric Oxide Donor, on Outcome After Stroke

Subgroup Analysis of the Efficacy of Nitric Oxide in Stroke (ENOS) Trial

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Background and Purpose—Nitric oxide donors are candidate treatments for acute stroke, potentially through hemodynamic, reperfusion, and neuroprotectant effects, especially if given early. Although the large Efficacy of Nitric Oxide in Stroke (ENOS) trial of transdermal glyceryl trinitrate (GTN) was neutral, a prespecified subgroup suggested that GTN improved functional outcome if administered early after stroke onset.

Methods—Prospective analysis of subgroup of patients randomized into the ENOS trial within 6 hours of stroke onset. Safety and efficacy of GTN versus no GTN were assessed using data on early and late outcomes.

Results—Two hundred seventy-three patients were randomized within 6 hours of ictus: mean (SD) age, 69.9 (12.7) years; men, 154 (56.4%); ischemic stroke, 208 (76.2%); Scandinavian Stroke Scale, 32.1 (11.9); and total anterior circulation syndrome, 86 (31.5%). When compared with no GTN, the first dose of GTN lowered blood pressure by 9.4/3.3 mm Hg ($P<0.01$, $P=0.064$) and shifted the modified Rankin Scale to a better outcome by day 90, adjusted common odds ratio, 0.51 (95% confidence interval, 0.32–0.80). Significant beneficial effects were also seen with GTN for disability (Barthel Index), quality of life (EuroQol-Visual Analogue Scale), cognition (telephone Mini-Mental State Examination), and mood (Zung Depression Scale). GTN was safe to administer with less serious adverse events by day 90 (GTN 18.8% versus no GTN 34.1%) and death (hazard ratio, 0.44; 95% confidence interval, 0.20–0.99; $P=0.047$).

Conclusions—In a subgroup analysis of the large ENOS trial, transdermal GTN was safe to administer and associated with improved functional outcome and fewer deaths when administered within 6 hours of stroke onset.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00989716.

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Key Words: blood pressure ■ cerebral hemorrhage ■ nitroglycerin ■ nitric oxide ■ stroke

Treatment options for acute ischemic stroke are limited to thrombolysis, aspirin, hemicraniectomy and stroke unit care,[1–4] and mechanical thrombectomy.[5–7] Although there are no definitive treatments for acute intracerebral hemorrhage, lowering blood pressure (BP) might be beneficial.[8] As a result, new interventions are still needed and, ideally, ones that are simple to administer and relevant irrespective of stroke type so that they can be given prehospital or immediately on admission to hospital before neuroimaging.

Nitric oxide (NO) donors are a candidate treatment for acute stroke.[9–11] In preclinical studies, NO donors reduced lesion size and increased cerebral blood flow, but only if given early.[12] In multiple pilot randomized controlled trials, NO donors (specifically intravenous sodium nitroprusside and transdermal glyceryl trinitrate [GTN]) reduced BP, pulse pressure, variability, and peak systolic BP; maintained cerebral blood flow (in spite of BP reduction); and improved arterial compliance.[13–17] Although sodium nitroprusside attenuated platelet function, GTN had no effect on platelets,[13,14] suggesting that it could be given to patients whether they had ischemic or hemorrhagic stroke. In a small trial of GTN administered by paramedics before hospital admission (with median time to

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Table 1. Baseline Characteristics in Patients Randomized Within 6 Hours by Treatment Group and Those Randomized Beyond 6 Hours

	GTN	No GTN	All <6 h	All >6 h	2p
No. of patients	144	129	273	3738	
Age, y*	69.0 (11.7)	70.8 (13.6)	69.9 (12.7)	70.3 (12.1)	0.55
Sex, men (%)*	75 (52.1)	79 (61.2)	154 (56.4)	2143 (57.3)	0.77
Geographical region					
Asia	7 (4.9)	9 (7.0)	16 (5.9)	543 (14.5)	<0.001
Europe	30 (20.8)	16 (12.4)	46 (16.8)	601 (16.1)	0.74
United Kingdom	76 (52.8)	79 (61.2)	155 (56.8)	2390 (63.9)	0.018
Other	31 (21.5)	25 (19.4)	56 (20.5)	204 (5.5)	<0.001
mRS>0*	26 (18.1)	28 (21.7)	54 (19.8)	972 (26.0)	0.023
Medical history (%)					
Hypertension	95 (66.0)	73 (56.6)	168 (61.5)	2439 (65.2)	0.21
Treated hypertension	80 (55.6)	63 (48.8)	143 (52.4)	1995 (53.4)	0.75
Hyperlipidemia	40 (27.8)	24 (18.6)	64 (23.4)	1034 (27.7)	0.28
Atrial fibrillation	28 (19.4)	22 (17.1)	50 (18.3)	712 (19.0)	0.77
Diabetes mellitus*	22 (15.3)	15 (11.6)	37 (13.6)	662 (17.7)	0.08
Previous stroke*	27 (18.8)	12 (9.3)	39 (14.3)	555 (14.8)	0.80
TIA	23 (16.0)	20 (15.5)	43 (15.8)	501 (13.4)	0.49
IHD	20 (13.9)	14 (10.9)	34 (12.5)	635 (17.0)	0.15
PAD	5 (3.5)	3 (2.3)	8 (2.9)	109 (2.9)	0.88
Smoking, current	31 (22.0)	27 (22.1)	58 (22.1)	887 (24.8)	0.61
Alcohol >21 upw	9 (6.3)	12 (9.3)	21 (7.7)	273 (7.3)	0.84
Nitrate therapy*	5 (3.5)	2 (1.6)	7 (2.6)	147 (3.9)	0.26
Qualifying event (%)*					
Ischemic stroke	113 (78.5)	95 (73.6)	208 (76.2)	3134 (83.8)	0.001
Hemorrhagic stroke	29 (20.1)	32 (24.8)	61 (22.3)	568 (15.2)	0.002
Stroke type unknown	0	0	0	1 (0.0)	0.79
Nonstroke	2 (1.4)	2 (1.6)	4 (1.5)	35 (0.9)	0.39
Side of lesion, right (%)	75 (52.1)	75 (58.1)	150 (54.9)	1936 (51.9)	0.56
SSS (of 58)*	33.2 (11.5)	30.9 (12.3)	32.1 (11.9)	33.8 (13.3)	0.022
NIHSS (of 42)[23]	11.4 (4.9)	12.4 (5.3)	11.9 (5.1)	11.1 (5.7)	0.022
GCS<15 (%)	43 (29.9)	50 (38.8)	93 (34.1)	1136 (30.4)	0.20
Clinical syndrome[28]					
TACS*	43 (29.9)	43 (33.3)	86 (31.5)	1123 (30.0)	0.61
PACS	57 (39.6)	55 (42.6)	112 (41.0)	1139 (30.5)	<0.001
LACS	37 (25.7)	25 (19.4)	62 (22.7)	1335 (35.7)	<0.001
POCS	7 (4.9)	6 (4.7)	13 (4.8)	141 (3.8)	0.41
IS cause					
Cardioembolic	34 (30.1)	26 (27.4)	60 (28.8)	657 (21.0)	0.007
Large vessel	22 (19.5)	16 (16.8)	38 (18.3)	704 (22.5)	0.16
Small vessel disease	41 (36.3)	31 (32.6)	72 (34.6)	1204 (38.4)	0.27
Other	20 (17.7)	21 (22.1)	41 (19.7)	621 (19.8)	0.97
Hemodynamics					
BP, systolic, mm Hg*	167.5 (18.7)	165.9 (17.7)	166.7 (18.2)	167.3 (19.0)	0.64
BP, diastolic, mm Hg	91.7 (13.7)	89.8 (12.9)	90.8 (13.3)	89.4 (13.1)	0.089
Heart rate, bpm	78.8 (15.3)	76.1 (14.4)	77.5 (14.9)	77.5 (14.7)	0.99
OTR, h*	4.6 [1.8]	4.5 [1.9]	4.6 [1.8]	27.0 [19.2]	<0.001
Thrombolysis (%)*	50 (34.7)	43 (33.3)	93 (34.1)	332 (8.9)	<0.001

(*Continued*)

Table 1. Continued

	GTN	No GTN	All <6 h	All >6 h	2p
Continue/stop randomization					
Continue	33 (22.9)	35 (27.1)	68 (24.9)	985 (26.4)	0.60
Stop	47 (32.6)	28 (21.7)	75 (27.5)	969 (25.9)	0.57
Not relevant	64 (44.4)	66 (51.2)	130 (47.6)	1784 (47.7)	0.97
Baseline scan (%)					
Visible infarction	40 (27.8)	46 (35.7)	86 (31.5)	2041 (54.6)	<0.001
Visible hemorrhage	28 (19.4)	30 (23.8)	58 (21.2)	573 (15.3)	0.01
No lesion seen	75 (52.1)	49 (38.9)	124 (45.4)	1091 (29.2)	<0.001
Nonstroke lesion	1 (0.7)	1 (0.8)	2 (0.7)	14 (0.4)	0.36

Data are number (%), median [interquartile range], or mean (SD). Comparisons are between those randomized within and beyond 6 hours. 2p indicates two-sided *P* value; BP, blood pressure; GCS, Glasgow Coma Scale; IHD, ischemic heart disease; IS, ischemic stroke; LACS, lacunar syndrome; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OTR, time from onset to randomization; PACS, partial anterior circulation syndrome; PAD, peripheral artery disease; POCS, posterior circulation syndrome; SSS, Scandinavian Stroke Scale; TACS, total anterior circulation syndrome; TIA, transient ischemic attack; and upw, units per week.

*Variable used in statistical adjustment.

admission of 55 minutes), GTN seemed to improve functional outcome, assessed as the modified Rankin Scale (mRS).[17] When assessed in a large international trial involving patients with stroke within 48 hours, GTN was safe to administer but did not alter mRS, the primary outcome.[18]

The potential benefit of GTN when administered early[17] suggested that the effect of GTN on outcome should be tested in patients enrolled early into ENOS, as identified prospectively in the statistical analysis plan before database lock and unblinding of data.[19] When assessed as the interaction between treatment, mRS, and time to randomization, GTN improved mRS in the subgroup of patients randomized within 6 hours into ENOS (identified here-on as ENOS-early).[18] The present article examines this finding in further detail.

Methods

ENOS Trial

The protocol, statistical analysis plan, baseline characteristics, and main results for ENOS have been published previously.[18–21] In brief, ENOS examined the safety and efficacy of GTN versus no GTN (single-blind delivery) in patients with acute ischemic or hemorrhagic stroke. Patients who were taking antihypertensive therapy immediately before their stroke were also randomized to continue or stop their therapy (open-label) in a partial factorial design. Both sets of interventions were given for 7 days. The primary outcome was the mRS assessed by masked central telephone call at day 90. The trial recruited 4011 patients from 173 sites across 23 countries in 5 continents.[21] Although the trial was neutral for both interventions, patients randomized to GTN within 6 hours, a prespecified subgroup,[19] had a better functional outcome than those assigned to no GTN; this subgroup is the subject of this publication.

Outcomes

The primary outcome was the 7-level mRS,[18] as recommended by the European Stroke Organisation,[22] with assessment at day 90. The effect of treatment on mRS was assessed in prespecified subgroups: age, sex, history of hypertension, previous stroke, atrial fibrillation, nitrate use, systolic BP, stroke type, stroke severity, stroke syndrome, presence of ipsilateral carotid stenosis, use of alteplase, and randomization to continue versus stop prestroke antihypertensive medication. Secondary outcomes at day 7 included: intracerebral hemorrhage, recurrent stroke, deterioration,[19] and impairment (Scandinavian Stroke Scale [SSS] and calculated National Institutes of Health Stroke Scale [NIHSS][23]). Resource utilization was assessed on discharge from (or death in) hospital: length of stay; assessment/treatment by a physiotherapist, occupational therapist, or speech therapist; and discharge destination (ordered categorical scale: died in hospital, still in hospital, in rehabilitation hospital, in nursing home, in residential home, at carer's home, or at home alone or with partner-carer). Secondary outcomes at day 90 included: activities of daily living (Barthel Index [BI] out of 100), quality of life (health utility status, derived from EuroQol-5 dimensions-3 levels [EQ-5D]; EQ-Visual Analogue Scale), cognition (telephone Mini-Mental State Examination [tMMSE]; Telephone Interview Cognition Scale; category fluency as animal naming), mood (Zung Depression Scale, short-form[24]), recurrent stroke, and disposition (died, still in hospital, readmitted to hospital, in nursing home, in residential home, at carer's home, at home alone, or with partner-carer). Safety measures included all-cause deaths and serious adverse events, the latter coded in an ordered categorical scale[25]: fatal serious adverse event (SAE), nonfatal SAE, and no SAE; and headache, hypotension, and hypertension by day 7.

Statistics

Because an intervention could reduce dependency but increase death, all ordinal or continuous measures included a score for death, as is standard for mRS and EQ-5D/health utility status. Death was coded as −5 for BI; −1 for animal naming, EQ-Visual Analogue Scale, MMSE, and Telephone Interview Cognition Scale; 0 for EQ-5D/health utility status; 6 for mRS; and 102.5 for Zung Depression Scale.[26,27] Data are shown as number (%), median [interquartile range], or mean (SD). Comparisons between groups use binary logistic regression, Cox regression, ordinal logistic regression, or multiple linear regression; results are given as odds ratio or mean difference, with 95% confidence interval and significance; a P value <0.05 is considered significant. The assumption of proportionality of odds for ordinal logistic regression was tested using the likelihood ratio test. Subgroup analyses were performed by adding an interaction term to an adjusted ordinal logistic regression model. Analyses are shown both unadjusted, and adjusted for age, sex, premorbid mRS, previous stroke, history of diabetes mellitus, prior use of nitrates, final diagnosis, SSS, total anterior circulation syndrome, systolic BP, use of thrombolysis, feeding status, time to randomization, and randomization to continue versus stop prestroke antihypertensive treatment. Ordinal numbers-needed-to-treat were calculated as published and signify the number of people who need to be treated for one of them to move by one or more levels of outcome, for example, from mRS score 4 to 3 or lower. Analyses were performed using SAS version 9.3.

Results

Patients

The characteristics of the 273 patients recruited into ENOS within 6 hours of stroke onset (ENOS-early, median 4.6 hours) are shown in Table 1. Of these, 144 were randomized to GTN and 129 to no GTN. The mean age was 69.9 (12.7) years, 154 (56.4%) were men, 155 (56.8%) were recruited from the United Kingdom, and 208 (76.2%) had an ischemic stroke. The mean baseline SSS was 32.1 (11.9) of 58, 86 (31.5%) had a total anterior circulation syndrome, and mean BP was 166.7 (18.2)/90.8 (13.3) mm Hg; 93 (34.1%) patients also received intravenous thrombolysis (Table 1). In comparison with patients recruited between 6 and 48 hours, those randomized within 6 hours were more likely to have an ICH, more severe stroke, a cardioembolic cause for ischemic stroke, and receive thrombolysis.

Table 2. Primary and Secondary Outcomes, and Safety Measures, at Days 7 and 90

	All	GTN	No GTN	OR/MD (95% CI)	2p
Modified Rankin Scale	273	144	129	…	…
Median (of 6), primary outcome	3 [3]	3 [3]	3 [3]	0.51 (0.32 to 0.80)	0.004
mRS score >2, adjusted	152 (55.7)	74 (51.4)	78 (60.5)	0.60 (0.32 to 1.13)	0.11
Day 7	270	144	126	…	…
SICH (%)	11 (4.1)	7 (4.9)	4 (3.2)	2.11 (0.37 to 11.99)	0.40
Recurrent stroke (%)	9 (3.3)	3 (2.1)	6 (4.8)	0.29 (0.05 to 1.74)	0.17
Deterioration (%)[19]	36 (13.3)	15 (10.4)	21 (16.7)	0.57 (0.24 to 1.34)	0.20
SSS (of 58)	38.7 (17.5)	40.8 (16.2)	36.3 (18.7)	4.52 (0.34 to 8.70)	0.17
NIHSS (of 42)[23]	9.0 (7.5)	8.1 (7.0)	10.1 (8.0)	−1.94 (−3.74 to −0.15)	0.17
Hospital and discharge	268	143	125	…	…
Length of stay, d	16.6 (20.8)	15.5 (20.4)	17.8 (21.3)	−2.31 (−7.32 to 2.71)	0.74
Death or institution (%)	98 (36.6)	48 (33.6)	50 (40.0)	0.88 (0.49 to 1.60)	0.68
Day 90	273	144	129	…	…
Barthel Index (of 100)	67.2 (38.2)	73.6 (34.4)	60.1 (41.0)	13.53 (4.56 to 22.51)	0.007
Barthel Index <60 (%)	83 (30.4)	33 (22.9)	50 (38.8)	0.51 (0.25 to 1.06)	0.071
EQ-5D/HUS (of 1)	0.5 (0.4)	0.5 (0.4)	0.4 (0.4)	0.09 (−0.01 to 0.18)	0.32
EQ-VAS (of 100; n=256)	57.8 (32.0)	62.2 (28.9)	52.6 (34.7)	9.62 (1.79 to 17.45)	0.034
MMSE (n=192)	11.1 (7.0)	12.8 (6.0)	9.4 (7.5)	3.44 (1.51 to 5.37)	0.008
TICS-M (n=190)	13.8 (8.8)	16.1 (8.0)	11.4 (9.0)	4.76 (2.32 to 7.20)	<0.001
Verbal fluency (of ∞; n=193)	10.2 (7.4)	11.7 (6.7)	8.8 (7.8)	2.94 (0.88 to 5.01)	0.056
ZDS (of 100; n=229)	57.0 (24.8)	52.2 (21.2)	62.5 (27.6)	−10.30 (−16.66 to −3.94)	0.001
Recurrent stroke (%)	11 (4.0)	4 (2.8)	7 (5.4)	0.30 (0.06 to 1.54)	0.15
Carotid endarterectomy (%)	3 (1.1)	3 (2.1)	0 (0)	0 (0 to ∞)	1
Death or institution (%)	75 (27.5)	32 (22.2)	43 (33.3)	0.60 (0.30 to 1.18)	0.14
Safety					
Patients with SAE (%)					
Day 7	37 (13.6)	15 (10.4)	22 (17.1)	0.53 (0.24 to 1.19)	0.12
Day 90	71 (26.0)	27 (18.8)	44 (34.1)	0.41 (0.21 to 0.79)	0.008
Died (%)					
By day 7	11 (4.1)	5 (3.5)	6 (4.8)	0.87 (0.09 to 8.39)	0.91
In hospital	25 (9.3)	8 (5.6)	17 (13.6)	0.34 (0.10 to 1.22)	0.099
By day 90	37 (13.6)	11 (7.6)	26 (20.2)	0.31 (0.11 to 0.91)	0.033
Day 7 (%)					
Headache	37 (13.7)	25 (17.4)	12 (9.5)	1.89 (0.83 to 4.31)	0.13
Hypotension	9 (3.3)	6 (4.2)	3 (2.4)	1.84 (0.35 to 9.79)	0.48
Hypertension	25 (9.3)	12 (8.3)	13 (10.3)	0.66 (0.26 to 1.67)	0.38

Data are number (%), median [interquartile range], or mean (SD). Comparisons between groups are binary logistic regression, ordinal logistic regression, or multiple regression; results are odds ratio or mean difference, with 95% CIs and significance. 2p indicates two-sided *P* value; CI, confidence interval; EQ-5D, EuroQol-5 dimensions-3 levels; EQ-VAS, EQ-Visual Analogue Scale; HUS, health utility status; MD, mean difference; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SAE, serious adverse event; SICH, symptomatic intracranial hemorrhage; SSS, Scandinavian Stroke Scale; TICS-M, Telephone Interview Cognition Scale-Modified; and ZDS, Zung Depression Scale.

Outcomes

When compared with no GTN, the first dose of GTN lowered BP by 9.4 (21.4)/3.3 (14.6) mm Hg ($P<0.01$, $P=0.064$). By day 7, there were no differences between the treatment groups with respect to rates of symptomatic intracerebral hemorrhage, recurrence or deterioration, or impairment (SSS; Table 2). Similarly, length of hospital stay, and death in hospital or institutionalization from hospital, did not differ between the groups. A trend to fewer patients receiving physiotherapy was present in the GTN group: 105 (73.4%) versus no GTN 100 (80.0%), odds ratio, 0.51 (0.25–1.06); $P=0.071$. There was no difference in involvement by occupational therapists or speech therapists in hospital.

At day 90, patients randomized early to GTN had a significant shift to a lower/better mRS (primary outcome measure) whether assessed in adjusted (common odds ratio, 0.51; 95% confidence interval, 0.32–0.80) or unadjusted analyses (Figure 1). The mean mRS score for GTN versus no GTN was 2.6 (1.8) versus 3.2 (1.9), mean difference, 0.65 (95% confidence interval, 0.22–1.08; $P=0.003$; Table 2). The ordinal number-needed-to-treat, that is, number of patients needing treatment for a patient to transition a mRS level, was 5.2 (95% confidence interval, 3.3–13.1; Table I in the online-only Data Supplement). When the effect of treatment on outcome in prespecified subgroups was assessed, a nonsignificant trend was seen in favor of men responding to GTN; no significant interactions were present for stroke type, stroke severity, stroke syndrome,[28] systolic BP, or use of alteplase (Figure 2).

In comparison with no GTN, GTN was associated with significant shifts to better activities of daily living (higher BI), quality of life (higher EQ-Visual Analogue Scale), cognition (higher tMMSE and Telephone Interview Cognition Scale), and less mood disturbance (lower Zung Depression Scale). When assessed on an ordered categorical scale, patients randomized to GTN were more likely to be discharged to a preferable destination (Figure I in the online-only Data Supplement). Number-needed-to-treat varied between 3.7 and 7.1 for these outcomes (Table I in the online-only Data Supplement), and ordinal number needed to treat were lower than binary number needed to treat in each case.

GTN was safe to administer, being associated with fewer SAEs, whether assessed by frequency (Table 2) or by severity using an ordered categorical scale (Figure II in the online-only Data Supplement). Similarly, GTN was associated with fewer deaths during follow-up (Figure 3) and with trends to fewer deaths at earlier time points. GTN was associated with a trend to more headaches (Table 2).

Discussion

This subgroup analysis builds on the observation in the main ENOS trial that those patients who were randomized to transdermal GTN versus no GTN within 6 hours of stroke onset had an improved functional outcome (mRS, Figure 3[21]). In addition to the shift in mRS, early treatment with GTN was associated with improvements in activities of daily living (BI), quality of life (EQ-Visual Analogue Scale), cognition (tMMSE and Telephone Interview Cognition Scale), and mood (Zung Depression Scale) at 90 days. In addition, GTN was safe to administer to patients with hyperacute stroke with reduced rates of death and patients with ≥1 SAEs. No significant interactions were seen for mRS between GTN and any prespecified subgroup, including stroke type (ischemic and hemorrhagic stroke), stroke severity, stroke syndrome,[28] systolic BP, or use of alteplase; a nonsignificant trend to men responding to GTN more than women may reflect chance because a significant interaction in the opposite direction was seen across the whole trial.[18]

These positive data replicate the results of a small (n=41) ambulance-based paramedic-delivered randomized controlled trial of transdermal GTN (RIGHT[29]), where treatment was initiated in the ambulance by paramedics, on average, at 55 minutes after stroke onset. In comparison with no GTN, the NO donor was associated with improved functional outcome (mRS), and trends in favor of improved activities of daily living (BI), cognition (MMSE) and quality of life (EQ-5D), and fewer deaths.[17] The results of both RIGHT and ENOS-early are compatible with earlier preclinical studies in experimental models of ischemic stroke, whereby NO donors were effective at reducing lesion size, but only if administered early after stroke onset.[12]

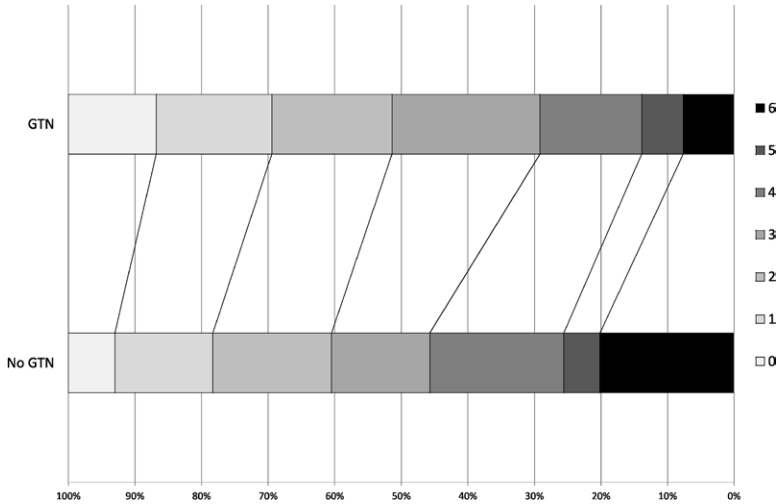

Figure 1. Comparison in distribution of 7-level modified Rankin Scale between glyceryl trinitrate (GTN) and no GTN at day 90: adjusted common odds ratio, 0.51 (95% confidence interval, 0.32–0.80; $P=0.004$); unadjusted common odds ratio, 0.55 (95% confidence interval, 0.36–0.84; $P=0.006$).

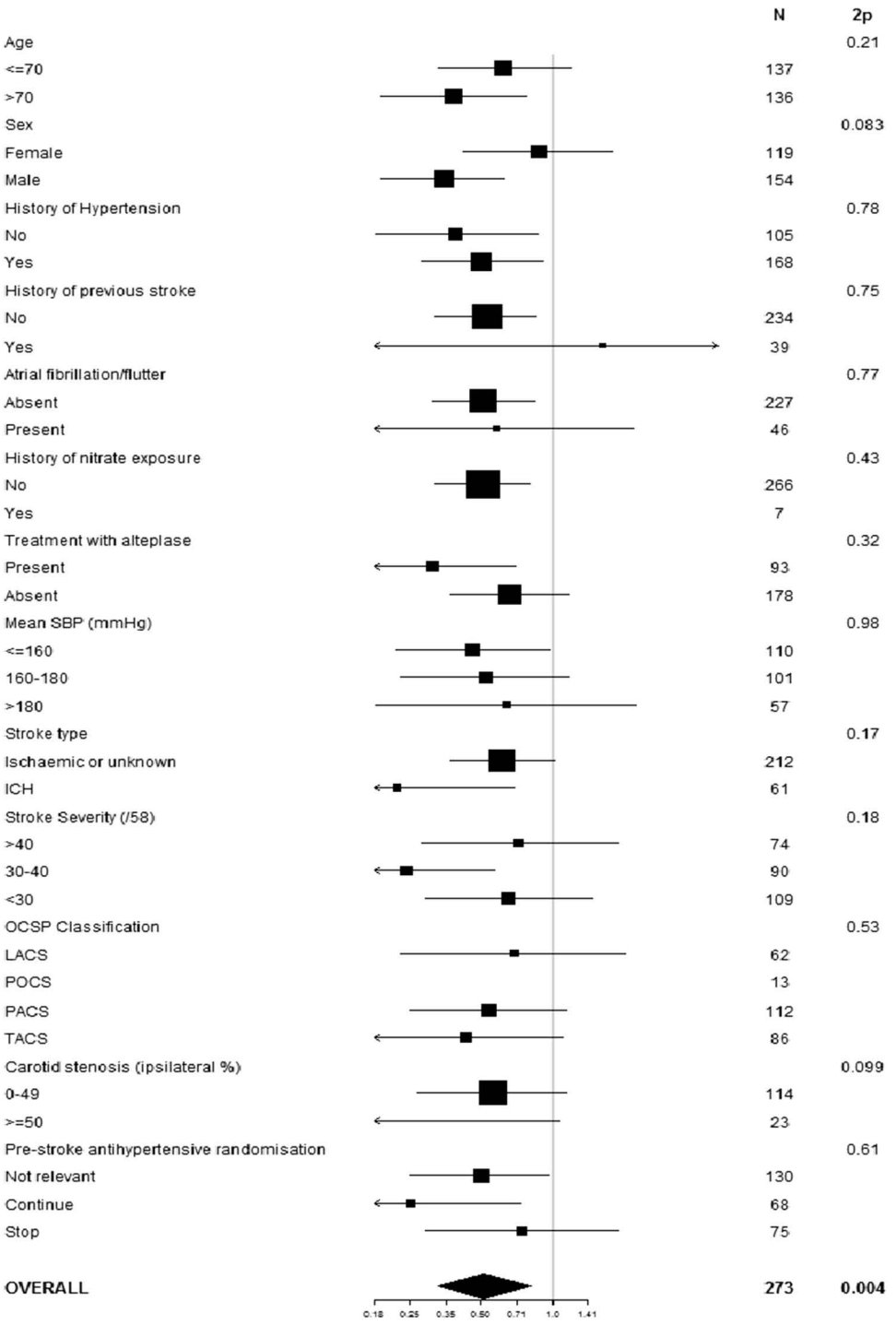

Figure 2. Subgroup analysis of effects on functional outcome at 90 days for glyceryl trinitrate (GTN) versus no GTN. Two-sided *P* values are for the adjusted interaction between subgroup and allocated treatment. ICH indicates intracerebral hemorrhage; LACS, lacunar syndrome; OCSP, Oxfordshire Community Stroke Project[28]; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; SBP, systolic blood pressure; and TACS, total anterior circulation syndrome.

The mechanisms by which NO donors in general, and GTN specifically, might improve outcome in patients with hyperacute stroke remain to be elucidated but several potential actions may be relevant, these comprising direct actions of GTN/NO donors and indirect actions whereby GTN enhances other treatments. First, high BP is associated with poor outcome in patients with stroke,[30] so lowering BP might be advantageous. Beneficial effects of BP lowering were suggested for intracerebral hemorrhage in the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial-2 (INTERACT-2) trial[8] but not in the ICH subgroup of SCAST.[31] No trial of patients with ischemic stroke or primarily of ischemic stroke has suggested benefit to date.[32–34] Hence, potential beneficial effects of lowering BP may be most relevant for ICH. Second, as an arterial vasodilator, GTN might improve cerebral blood flow, as seen in a pilot

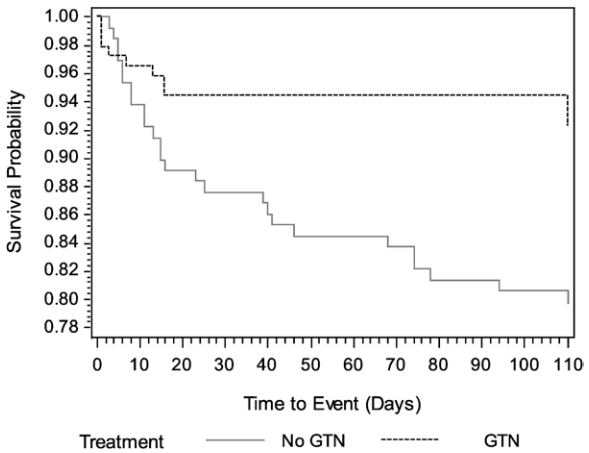

Figure 3. Survival curves over the 90 days of follow-up: glyceryl trinitrate (GTN) versus no GTN: hazard ratio, 0.44 (95% confidence interval, 0.20–0.99; *P*=0.047).

trial[16] and in preclinical stroke.[12] NO is a potent mediator of pial artery blood flow[35] so back-door reperfusion may occur via collaterals. Third, although the relevance of neuroprotection to human stroke remains unclear, NO donors did reduce lesion volume in preclinical stroke when administered early.[12] Fourth, through lowering systolic BP to <185 mm Hg, GTN may allow more patients to receive thrombolysis, and more quickly; trends to these findings were seen in the RIGHT pilot trial.[17] Fifth, GTN-induced arterial vasodilation might enhance access by endogenous and exogenous tissue-type plasminogen activator to clot thereby enhancing fibrinolysis. Finally, NO levels are low in patients with acute stroke[36,37] so replacing a key vasoactive and potentially neuroprotective endogenous molecule might be expected to be beneficial.

All these potential mechanisms imply that GTN will exhibit a time-dependent effect whereby early treatment is beneficial and later treatment is ineffective; such time dependency is present across trials of GTN with benefit in RIGHT and ENOS-early but not in the main part of ENOS or in 3 earlier pilot trials that recruited in the acute and subacute phase after stroke.[14–17]

This subgroup analysis of the ENOS trial has several strengths. First, the subgroup of patients who were randomized within 6 hours was prespecified,[19] so the presented analyses are not data-driven. Second, the results are compatible with earlier findings in the RIGHT pilot trial[17] and a meta-analysis of preclinical studies, the latter also showing a time-dependent effect.[12] Finally, the data come from a high fidelity trial with wide inclusion criteria and transcontinental recruitment[18] suggesting that the findings have external validity.

Nevertheless, 3 caveats need to be highlighted. First, the results come from a subgroup analysis; positive subgroups are common in large trials and yet most will be spurious and because of chance. Several trials have been performed chasing isolated positive subgroups in earlier studies and each was neutral, as seen for clomethizole,[38] fibroblast growth factor,[39] and surgery for intracerebral hemorrhage.[40,41] Second, the analysis is based on a small number (273) of patients, again raising the possibility of a false-positive result (type I error). Third, minor imbalances were present in baseline prognostic factors; in particular, patients randomized to GTN had less severe stroke apparent as a higher SSS and lower rates of cortical stroke syndromes. Finally, information was not collected a priori on newer interventions, such as hemicraniectomy and mechanical thrombectomy.

In summary, this prespecified subgroup analysis of patients recruited within 6 hours of stroke onset into the ENOS trial suggests that transdermal GTN improves functional and other clinical outcomes and reduces death and SAEs. Given that transdermal GTN is inexpensive (≈£5 per patient), safe, widely available and can be easily administered before hospitalization or brain imaging, these results, and those from the RIGHT pilot trial and a meta-analysis of preclinical stroke studies,[12,17] justify a further large study: the RIGHT-2 trial (http://right2-trial.org), which will further assess the safety and efficacy of GTN in 850 patients with ultra acute stroke who are recruited by paramedics in the prehospital ambulance environment using a protocol that builds on the earlier Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT), and Field Administration of Stroke Therapy–Magnesium (FAST-Mag) trial.[17,42,43]

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Disclosures

None.

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