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**Title**

Pre-hospital transdermal glyceryl trinitrate for ultra-acute ischaemic stroke: data from the RIGHT-2 randomised sham-controlled ambulance trial

**LIST OF SUPPLEMENTARY TABLES AND FIGURES**

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**Supplementary Table 1.** Adherence and reasons for non-adherence in patients with final diagnosis of ischaemic stroke by treatment group: glyceryl trinitrate (GTN) versus sham. Data are number (%).

	All	GTN	Sham
Participants with data	597	302	295
<b>Adherence (%), received</b>			
First treatment	596 (>99)	301 (>99)	295 (100)
At least first 2 days of treatment <sup>a</sup>	451 (76)	227 (75)	224 (76)
All 4 days treatment	307 (51)	146 (48)	161 (55)
<b>Reasons for non-adherence (%) <sup>b</sup></b>			
Non-stroke diagnosis initially	12 (2)	4 (1)	8 (3)
Serious adverse event	3 (1)	2 (1)	1 (<1)
Adverse event (not an SAE)	2 (<1)	2 (1)	0 (0)
Discharged before day 2	15 (3)	11 (4)	4 (1)
Participant/proxy refused patch	4 (1)	4 (1)	0 (0)
Medical decision to stop treatment	32 (5)	19 (6)	13 (4)
Procedural error	35 (6)	14 (5)	21 (7)
Trial medication missing/not available	13 (2)	6 (2)	7 (2)
Died	2 (<1)	1 (<1)	1 (<1)
Others	22 (4)	10 (3)	12 (4)

<sup>a</sup> Patients receiving at least the first two days of treatment are considered to have been adherent to treatment

<sup>b</sup> Reasons for non-adherence are not mutually exclusive

**Supplementary Table 2.** In hospital management and treatment for 597 participants with a final diagnosis of ischaemic stroke by treatment group: glyceryl trinitrate (GTN) versus sham. Data are number (%).

<b>Activity (%)</b>	<b>N</b>	<b>GTN</b>	<b>Sham</b>	<b>aOR/DIM (95% CI)</b>	<b>p-value</b>
Intravenous alteplase	597	150 (49.7)	134 (45.4)	10.91 (0.12, 977.7)	0.30
Door-to-needle time (mins)	284	49 [40, 66]	54 [43, 69]	3.5 (-1, 8)	0.15
Thrombectomy	589	7 (2.3)	17 (5.8)	0.35 (0.14, 0.87)	0.024
Carotid endarterectomy	589	1 (0.3)	2 (0.7)	0.11 (0.00, 6.48)	0.28
Hemicraniectomy	588	0 (0)	1 (0.3)	-	-
Other surgery	588	1 (0.3)	0 (0)	-	-
Neurosurgical Unit	590	5 (1.7)	8 (2.7)	0.80 (0.22, 2.97)	0.74
Ventilation	589	4 (1.3)	2 (0.7)	1.79 (0.28, 11.54)	0.54
Acute Stroke Unit	592	264 (88.3)	261 (89.1)	1.03 (0.61, 1.76)	0.91
Stroke Rehabilitation Unit	593	92 (30.7)	113 (38.6)	0.71 (0.50, 1.01)	0.055
Physiotherapy	592	265 (88.6)	263 (89.8)	0.99 (0.58, 1.69)	0.97
Occupational therapy	590	254 (85.2)	249 (85.3)	1.04 (0.65, 1.66)	0.87
Speech therapy	590	212 (71.1)	217 (74.3)	0.94 (0.64, 1.37)	0.73

DIM: difference in medians; aOR: adjusted odds ratio.

**Supplementary Table 3.** Relationship between imaging characteristics on admission and death, and modified Rankin Scale score, at day 90 in 597 participants with a final diagnosis of ischaemic stroke. Data are odds ratio (OR) or hazard ratio (HR). Analyses use binary logistic regression, Cox proportional hazards regression or ordinal logistic regression and are unadjusted.

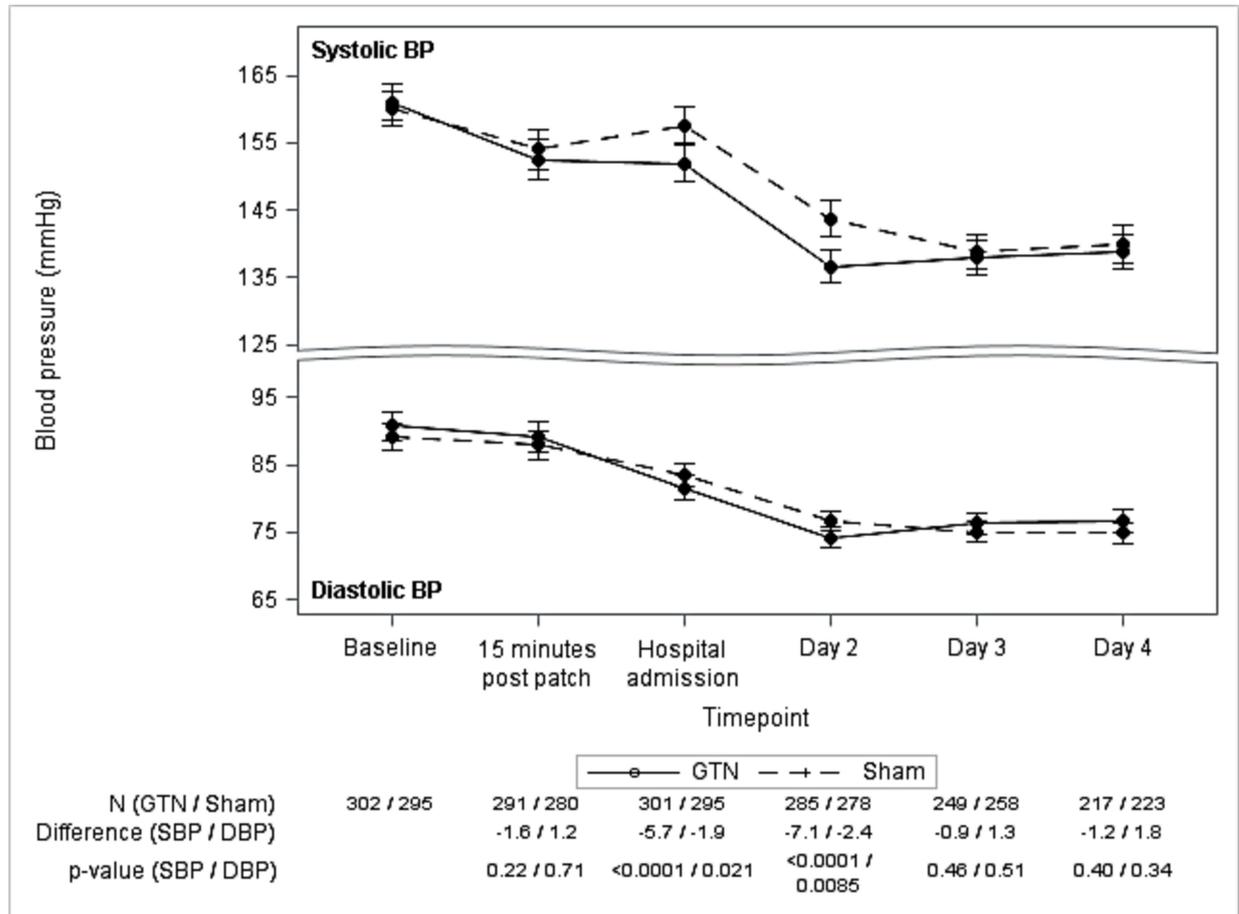
	Death			mRS		
	HR (95% CI)	p	p†	OR (95% CI)	p	p†
Patients with data	597			597		
Patients with outcome	589			580		
<b>Pre-stroke neuroimaging</b>						
Atrophy	1.28 (0.47, 3.46)	0.63	0.65	1.62 (0.82, 3.20)	0.16	0.95
PVL	1.37 (0.94, 2.00)	0.098	0.89	2.06 (1.54, 2.77)	< 0.0001	0.83
Old vascular lesion(s)	1.37 (0.82, 2.26)	0.23	0.48	2.20 (1.52, 3.18)	< 0.0001	0.17
'Brain frailty' score	1.29 (1.00, 1.67)	0.048	0.71	1.77 (1.46, 2.13)	< 0.0001	0.39
SVD score	1.09 (0.86, 1.40)	0.48	0.41	1.55 (1.28, 1.88)	< 0.0001	0.57
<b>Acute neuroimaging changes</b>						
Infarct size [/5]	1.11 (0.89, 1.39)	0.34	0.96	1.18 (0.99, 1.40)	0.066	0.42
Degree of ischaemic change [0-2]	1.06 (0.84, 1.34)	0.62	0.71	1.10 (0.92, 1.32)	0.29	0.25
ASPECTS (/12)	0.91 (0.79, 1.05)	0.22	0.43	0.86 (0.76, 0.98)	0.022	0.62
Infarct swelling (%)	1.58 (1.04, 2.39)	0.031	0.78	1.53 (1.07, 2.19)	0.019	0.12
Mass effect [/6]	1.45 (1.12, 1.88)	0.0049	0.34	1.42 (1.12, 1.82)	0.0046	0.56
Hyperdense artery (%)	1.59 (1.01, 2.51)	0.046	0.37	1.55 (1.08, 2.22)	0.017	0.15
Arteries sum [0-7]	0.85 (0.62, 1.18)	0.34	0.72	0.89 (0.73, 1.09)	0.25	0.31
Q165						
Post-alteplase HTI (%)	6.36 (3.19, 12.69)	< 0.0001	0.59	8.63 (3.13, 23.75)	< 0.0001	0.63
Post-thrombectomy HTI (%)	-	-	-	-	-	-

<b>CTA</b>						
Hyperdense artery (%)	1.07 (0.31, 3.64)	0.92	0.64	2.29 (0.96, 5.44)	0.060	0.043
mTICI [0-5]	0.96 (0.68, 1.34)	0.79	0.84	1.02 (0.81, 1.28)	0.86	0.12
Mori [0-6]	0.92 (0.68, 1.25)	0.59	0.65	1.00 (0.82, 1.22)	1.00	0.22
Clot burden [0-10]	0.94 (0.81, 1.10)	0.44	0.89	1.03 (0.93, 1.13)	0.57	0.11
Arteries sum [0-7]	0.94 (0.63, 1.43)	0.78	0.90	1.04 (0.79, 1.37)	0.78	0.052
Collateral status [0-3]	0.86 (0.51, 1.45)	0.58	0.85	1.09 (0.79, 1.51)	0.59	0.14
<b>Carotid imaging</b>						
Stenosis >70% vs <30%	0.91 (0.12, 6.96)	0.93	0.99	1.33 (0.55, 3.22)	0.53	0.86

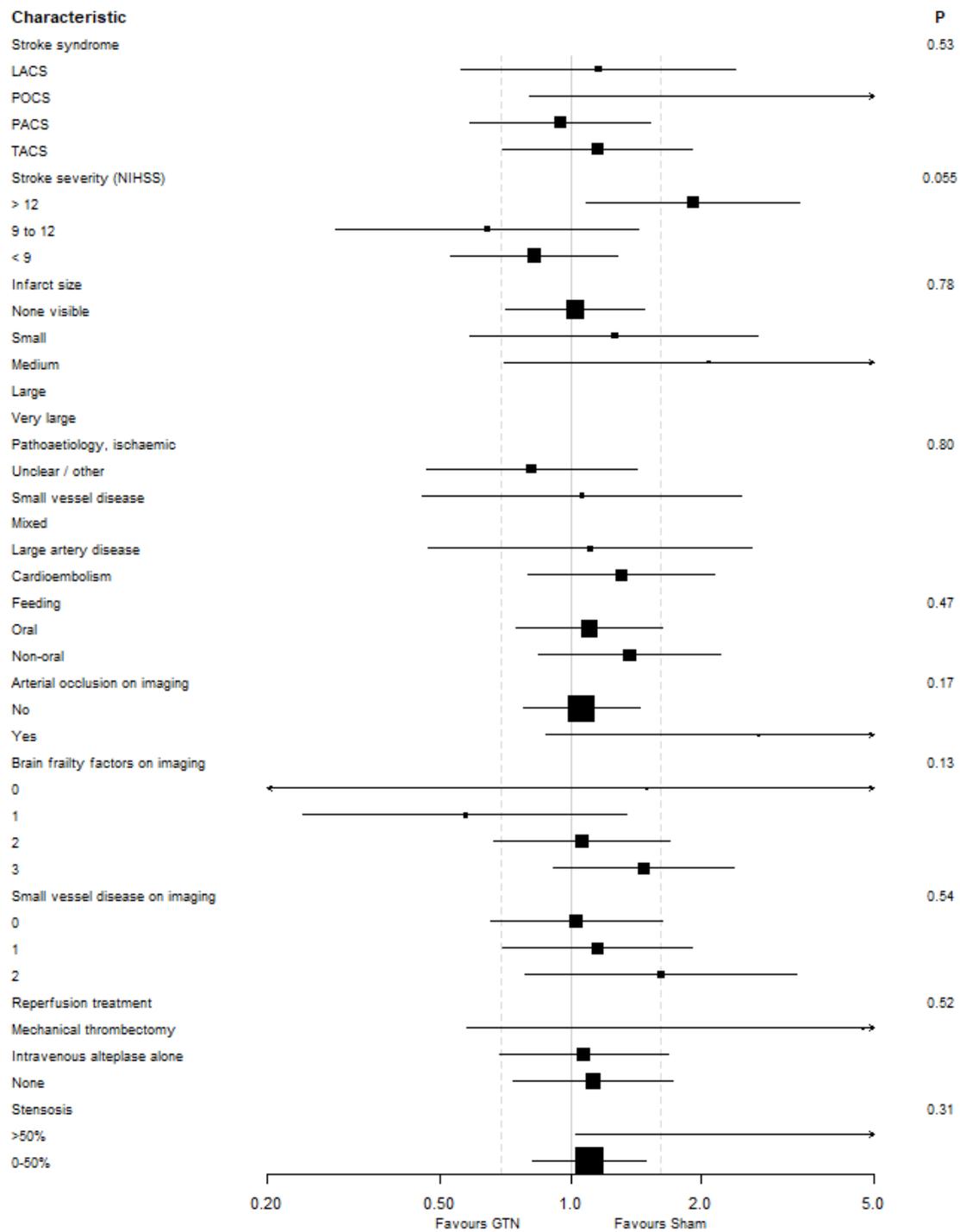
ASPECTS: Alberta Stroke Program Early CT Score; CTA: CT angiography; HTI: haemorrhagic transformation of infarct; mTICI: modified thrombolysis in cerebral infarction; PVL: periventricular lucencies; SVD: small vessel disease.

p†: p for interaction with GTN vs sham

**Supplementary Figure 1.** Blood pressure profile in 597 participants with a final diagnosis of ischaemic stroke by treatment group: glyceryl trinitrate (GTN) versus sham.

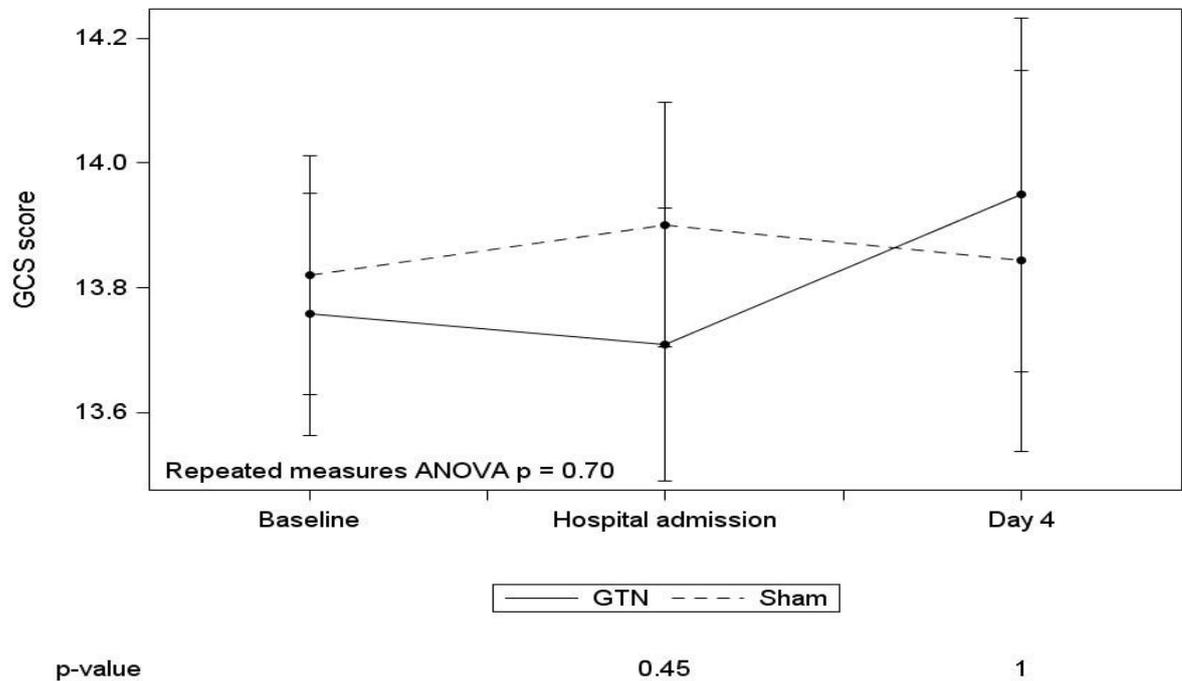


**Supplementary Figure 2.** Forest plot showing modified Rankin scale in *post hoc* subgroups of participants with ischaemic stroke, with p-value for interaction.

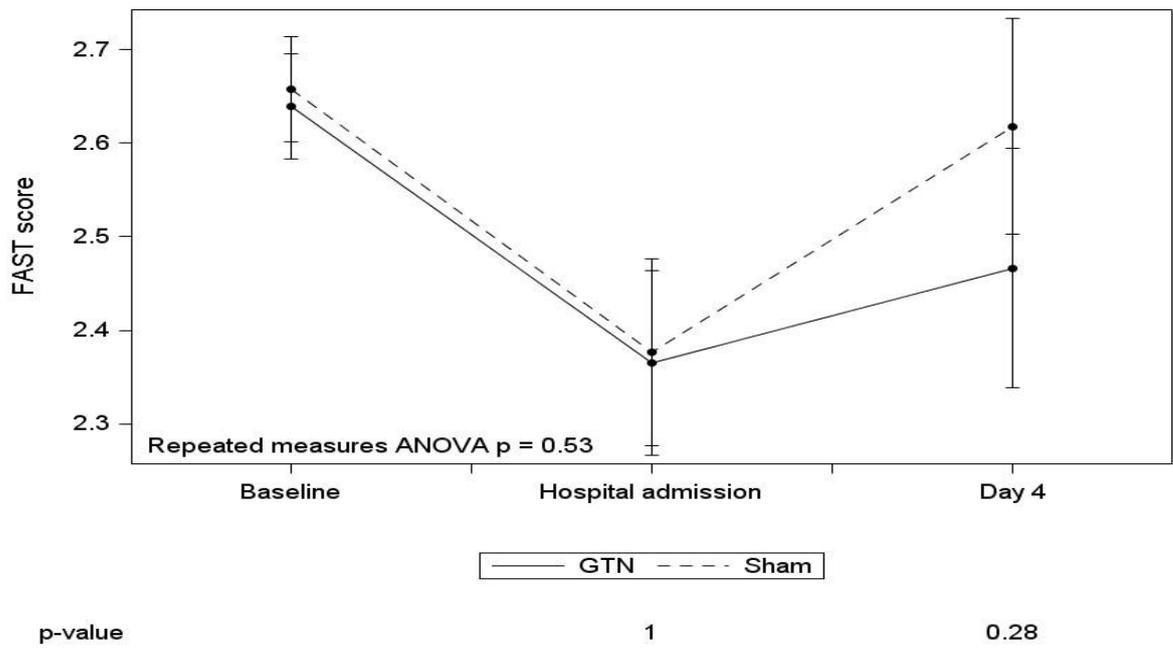


**Supplementary Figure 3.** Changes in Glasgow coma scale and Face-Arm-Speech test from baseline in ambulance 597 participants with a final diagnosis of ischaemic stroke by treatment group: glyceryl trinitrate (GTN) versus sham.

A) Glasgow coma scale (GCS) with Bonferroni corrected ANCOVA

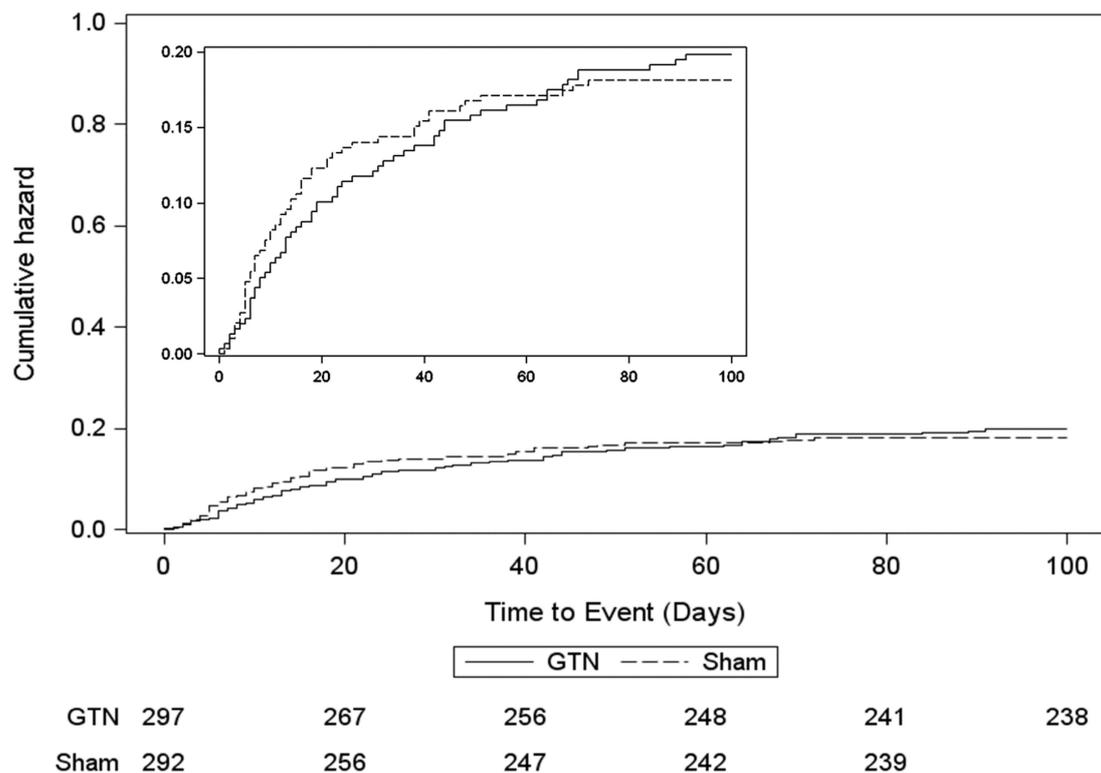


B) Face-Arm-Speech test with Bonferroni corrected ANCOVA



**Supplementary Figure 4.** Cumulative case fatality during the 90 days of follow-up after randomisation in 597 participants with a final diagnosis of ischaemic stroke by treatment group – glyceryl trinitrate (GTN) versus sham. Comparison of GTN versus sham by Cox regression with adjustment for age, sex, pre-morbid modified Rankin Scale, face-arm-speech time test, pre-treatment systolic BP, and time to randomisation.

Adjusted hazard ratio 1.24, 95% CI (0.85, 1.81),  $p=0.27$



**Supplementary Figure 5.** Forest plot of outcomes included in the global analysis (modified Rankin scale, Barthel index, Euro-Qol-5D, Zung depression scale, telephone interview cognition scale-modified – Wei-Lachin test) in 300 participants with a final diagnosis of ischaemic stroke by treatment group – glyceryl trinitrate (GTN) versus sham.

