

# 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

The ENOS Trial Investigators\*

## Summary

**Background** High blood pressure is associated with poor outcome after stroke. Whether blood pressure should be lowered early after stroke, and whether to continue or temporarily withdraw existing antihypertensive drugs, is not known. We assessed outcomes after stroke in patients given drugs to lower their blood pressure.

**Methods** In our multicentre, partial-factorial trial, we randomly assigned patients admitted to hospital with an acute ischaemic or haemorrhagic stroke and raised systolic blood pressure (systolic 140–220 mm Hg) to 7 days of transdermal glyceryl trinitrate (5 mg per day), started within 48 h of stroke onset, or to no glyceryl trinitrate (control group). A subset of patients who were taking antihypertensive drugs before their stroke were also randomly assigned to continue or stop taking these drugs. The primary outcome was function, assessed with the modified Rankin Scale at 90 days by observers masked to treatment assignment. This study is registered, number ISRCTN99414122.

**Findings** Between July 20, 2001, and Oct 14, 2013, we enrolled 4011 patients. Mean blood pressure was 167 (SD 19) mm Hg/90 (13) mm Hg at baseline (median 26 h [16–37] after stroke onset), and was significantly reduced on day 1 in 2000 patients allocated to glyceryl trinitrate compared with 2011 controls (difference –7.0 [95% CI –8.5 to –5.6] mm Hg/–3.5 [–4.4 to –2.6] mm Hg; both  $p < 0.0001$ ), and on day 7 in 1053 patients allocated to continue antihypertensive drugs compared with 1044 patients randomised to stop them (difference –9.5 [95% CI –11.8 to –7.2] mm Hg/–5.0 [–6.4 to –3.7] mm Hg; both  $p < 0.0001$ ). Functional outcome at day 90 did not differ in either treatment comparison—the adjusted common odds ratio (OR) for worse outcome with glyceryl trinitrate versus no glyceryl trinitrate was 1.01 (95% CI 0.91–1.13;  $p = 0.83$ ), and with continue versus stop antihypertensive drugs OR was 1.05 (0.90–1.22;  $p = 0.55$ ).

**Interpretation** In patients with acute stroke and high blood pressure, transdermal glyceryl trinitrate lowered blood pressure and had acceptable safety but did not improve functional outcome. We show no evidence to support continuing prestroke antihypertensive drugs in patients in the first few days after acute stroke.

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	Glyceryl trinitrate vs no glyceryl trinitrate analysis				Continue vs stop analysis					
	N	Glyceryl trinitrate (n=2000)	No glyceryl trinitrate (n=2011)	OR or MD (95% CI)	Two-sided p value	N	Continue (n=1053)	Stop (n=1044)	OR or MD (95% CI)	Two-sided p value
<b>Day 7 (or discharge)</b>										
Death, all cause	4001	61 (3%)	58 (3%)	1.12 (0.76–1.64)	0.57	2095	34 (3%)	27 (3%)	1.18 (0.69–2.00)	0.55
SSS score (out of 58)	3991	39.1 (1.6)	38.5 (1.6)	0.62 (–0.38 to 1.61)*	0.46	2088	37.1 (1.7)	38.4 (1.6)	–1.25 (–2.65 to 0.16)*	0.28
Neurological deterioration†	3991	177 (9%)	194 (10%)	0.88 (0.71–1.10)	0.28	2088	107 (10%)	105 (10%)	1.00 (0.74–1.34)	0.99
Recurrent stroke‡	3997	42 (2%)	31 (2%)	1.37 (0.85–2.20)	0.19	2093	30 (3%)	18 (2%)	1.64 (0.90–3.00)	0.10
Symptomatic intracranial haemorrhage‡	4000	22 (1%)	18 (1%)	1.20 (0.63–2.29)	0.59	2095	12 (1%)	11 (1%)	1.03 (0.43–2.44)	0.95
Headache‡	4000	360 (18%)	170 (9%)	2.39 (1.96–2.92)	<0.0001	2095	123 (12%)	117 (11%)	1.11 (0.84–1.47)	0.46
Hypotension‡	4000	53 (3%)	15 (1%)	3.55 (1.99–6.35)	<0.0001	2095	24 (2%)	16 (2%)	1.58 (0.82–3.02)	0.17
Hypertension‡	4000	138 (7%)	155 (8%)	0.87 (0.68–1.11)	0.26	2095	60 (6%)	94 (9%)	0.65 (0.46–0.92)	0.015
Serious adverse event	4011	271 (14%)	261 (13%)	1.05 (0.88–1.26)	0.59	2097	147 (14%)	155 (15%)	0.93 (0.73–1.19)	0.56
<b>Discharge data</b>										
Median hospital stay (days)	3985	11 (7–25)	11 (7–25)	–0.34 (–1.81 to 1.12)*	1.00	2086	12 (7–28)	11 (7–26)	1.20 (–0.88 to 3.28)*	0.32
Death or institution	3986	716 (36%)	761 (38%)	1.08 (0.94–1.25)	0.29	2086	450 (43%)	389 (37%)	0.76 (0.62–0.93)	0.008
<b>Day 90</b>										
Death	3996	233 (12%)	263 (13%)	0.89 (0.72–1.10)	0.27	2091	167 (16%)	146 (14%)	1.09 (0.83–1.42)	0.54
Death or institution	3980	554 (28%)	604 (30%)	0.88 (0.75–1.03)	0.11	2083	365 (35%)	323 (31%)	0.85 (0.69–1.06)	0.15
Barthel index (out of 100)	3970	66 (38)	63 (39)	2.18 (–0.23 to 4.59)*	0.11	2076	58 (41)	62 (39)	–3.83 (–7.29 to 0.38)*	0.098
Barthel index <60	3970	654 (33%)	699 (35%)	0.90 (0.76–1.06)	0.19	2076	425 (41%)	365 (35%)	1.28 (1.02–1.59)	0.031
t-MMSE score	2506	11 (7)	11 (7)	0.33 (–0.22 to 0.88)*	0.13	1272	9 (7)	10 (7)	–0.91 (–1.70 to 0.12)*	0.013
TICS-M score	2322	15 (10)	15 (10)	0.40 (–0.40 to 1.20)*	0.65	1179	13 (10)	15 (10)	–1.65 (–2.81 to 0.49)*	0.011
Verbal fluency score	2366	2.25 (3.04)	2.05 (2.92)	0.20 (–0.04 to 0.44)*	0.13	1201	1.9 (3.04)	2.25 (3.19)	–0.35 (–0.70 to 0.01)*	0.10
Health utility status	3952	0.49 (0.32)	0.48 (0.33)	0.01 (–0.01 to 0.03)*	0.87	2063	0.44 (0.33)	0.47 (0.33)	–0.03 (–0.06 to 0.00)*	0.24
EQ-VAS	3440	56.5 (30.8)	55.7 (31.6)	0.79 (–1.29 to 2.88)*	0.70	1759	51.8 (32.4)	54.2 (31.6)	–2.42 (–5.41 to 0.57)*	0.15
ZDS	3253	58.3 (23.7)	58.8 (24.6)	–0.50 (–2.15 to 1.16)*	0.82	1659	62.0 (24.9)	61.1 (24.6)	0.94 (–1.44 to 3.32)*	0.43
Serious adverse event	4011	510 (26%)	499 (25%)	1.04 (0.90–1.20)	0.62	2097	308 (29%)	286 (27%)	1.10 (0.91–1.33)	0.35

Data are number of patients (%) or mean (SD). OR=odds ratio. MD=mean difference. SSS=Scandinavian stroke scale. mRS=modified Rankin scale. t-MMSE=modified telephone mini-mental state examination. TICS-M=modified telephone interview for cognitive status. EQ=EuroQoL. VAS=visual analogue scale. ZDS=Zung depression scale. \*Values are MD. †Neurological deterioration was a decrease in SSS by more than 5 points and decrease in consciousness on SSS by more than 2 points. ‡Clinical events determined by the investigator.

Table 2: Secondary outcomes at days 7 and 90

	ENOS		Continue vs stop antihypertensive drugs	
	Glyceryl trinitrate	No glyceryl trinitrate	Continue	Stop
<b>Patient characteristics</b>				
Number of patients	2000	2011	1053	1044
Age (years)*	70 (12)	70 (12)	73 (11)	73 (11)
Men*	1147 (57%)	1150 (57%)	528 (50%)	540 (52%)
Pre-morbid mRS >0	490 (25%)	536 (27%)	365 (35%)	319 (31%)
<b>Time to random treatment assignment</b>				
Median time (h)*	26 (16–36)	26 (16–37)	26 (16–35)	26 (15–37)
Earlier than 6 h	144 (7%)	129 (6%)	68 (6%)	75 (7%)
<b>Geographical region†</b>				
Asia	276 (14%)	283 (14%)	102 (10%)	100 (10%)
UK	1272 (64%)	1273 (63%)	678 (64%)	674 (65%)
Rest of Europe	327 (16%)	325 (16%)	204 (19%)	203 (19%)
Other	130 (7%)	130 (7%)	69 (7%)	67 (6%)
<b>Medical history</b>				
Hypertension	1287 (64%)	1320 (66%)	1001 (95%)	993 (95%)
Taking antihypertensive drugs‡	1057 (53%)	1081 (54%)	1047 (99%)	1039 (99%)
Stroke	315 (16%)	279 (14%)	212 (20%)	204 (20%)
Transient ischaemic attack	275 (14%)	269 (13%)	181 (17%)	171 (16%)
Ischaemic heart disease	340 (17%)	329 (16%)	255 (24%)	268 (26%)
Peripheral arterial disease	51 (3%)	66 (3%)	37 (4%)	40 (4%)
Diabetes	343 (17%)	356 (18%)	240 (23%)	244 (23%)
Hyperlipidaemia§	552 (28%)	546 (27%)	395 (38%)	413 (40%)
Current smoker (n=3846, 96%)	459 (24%)	486 (25%)	185 (19%)	178 (18%)
Alcohol >21 units per week	140 (7%)	154 (8%)	57 (5%)	47 (5%)
Atrial fibrillation, current or previous	395 (20%)	367 (18%)	308 (29%)	258 (25%)
Nitrate use before stroke	87 (4%)	67 (3%)	70 (7%)	66 (6%)
<b>Haemodynamics</b>				
Systolic blood pressure (mm Hg)*	167 (19)	167 (19)	166 (19)	168 (19)
Diastolic blood pressure (mm Hg)	90 (13)	89 (13)	88 (13)	89 (13)
Mean heart rate (bpm; n=4007, 99.9%)	78 (15)	77 (15)	77 (15)	77 (15)

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	ENOS		Continue vs stop antihypertensive drugs	
	Glyceryl trinitrate	No glyceryl trinitrate	Continue	Stop
<b>Qualifying event*‡</b>				
Ischaemic stroke	1664 (83%)	1678 (83%)	928 (88%)	904 (87%)
Intracerebral haemorrhage	310 (16%)	319 (16%)	119 (11%)	127 (12%)
Stroke, type unknown	0	1 (<1%)	0	1 (<1%)
Non-stroke	26 (1%)	13 (1%)	6 (1%)	12 (1%)
Side of lesion, right (n=4003, 99.8%)	1023 (51%)	1063 (53%)	554 (53%)	520 (50%)
SSS score (out of 58)*¶	34 (13)	34 (13)	32 (14)	33 (13)
NIHSS (out of 42), estimated	11 (6)	11 (6)	12 (6)	11 (6)
GCS <3	607 (30%)	622 (31%)	364 (35%)	363 (35%)
<b>OCSF classification</b>				
Total anterior*	615 (31%)	594 (30%)	361 (34%)	336 (32%)
Partial anterior	616 (31%)	635 (32%)	349 (33%)	353 (34%)
Lacunar	695 (35%)	702 (35%)	301 (29%)	323 (31%)
Posterior	74 (4%)	80 (4%)	42 (4%)	32 (3%)
<b>Ischaemic causative mechanisms**</b>				
Cardioembolic	365 (22%)	352 (21%)	277 (30%)	230 (25%)
Large vessel	359 (22%)	383 (23%)	197 (21%)	220 (24%)
Small vessel	639 (38%)	637 (38%)	305 (33%)	321 (36%)
Other	342 (21%)	320 (19%)	170 (18%)	160 (18%)
Not determined	34 (2%)	44 (2%)	23 (2%)	14 (1%)
<b>Other treatment</b>				
Thrombolytic treatment*	204 (10%)	221 (11%)	123 (12%)	125 (12%)

Data are n (%), median (IQR), or mean (SD). Percentages exclude missing values from denominators. mRS=modified Rankin Scale. bpm=beats per min. SSS=Scandinavian Stroke Scale. NIHSS=National Institutes of Health Stroke Scale. GCS=Glasgow Coma Scale score. OCSF=Oxfordshire Community Stroke Project classification. \*Minimisation variable. †Stratification variable. ‡Qualifying event was determined from investigator information and blinded adjudication of brain neuroimaging. §Hyperlipidaemia defined locally. ¶Scores on the SSS range from 0 (coma with quadriplegia) to 58 (normal neurological status). ||Scores on the Glasgow Coma Scale range from 3 (deep coma) to 15 (fully conscious). \*\*Sum might be higher than 100% because of mixed causes.

Table 1: Baseline characteristics

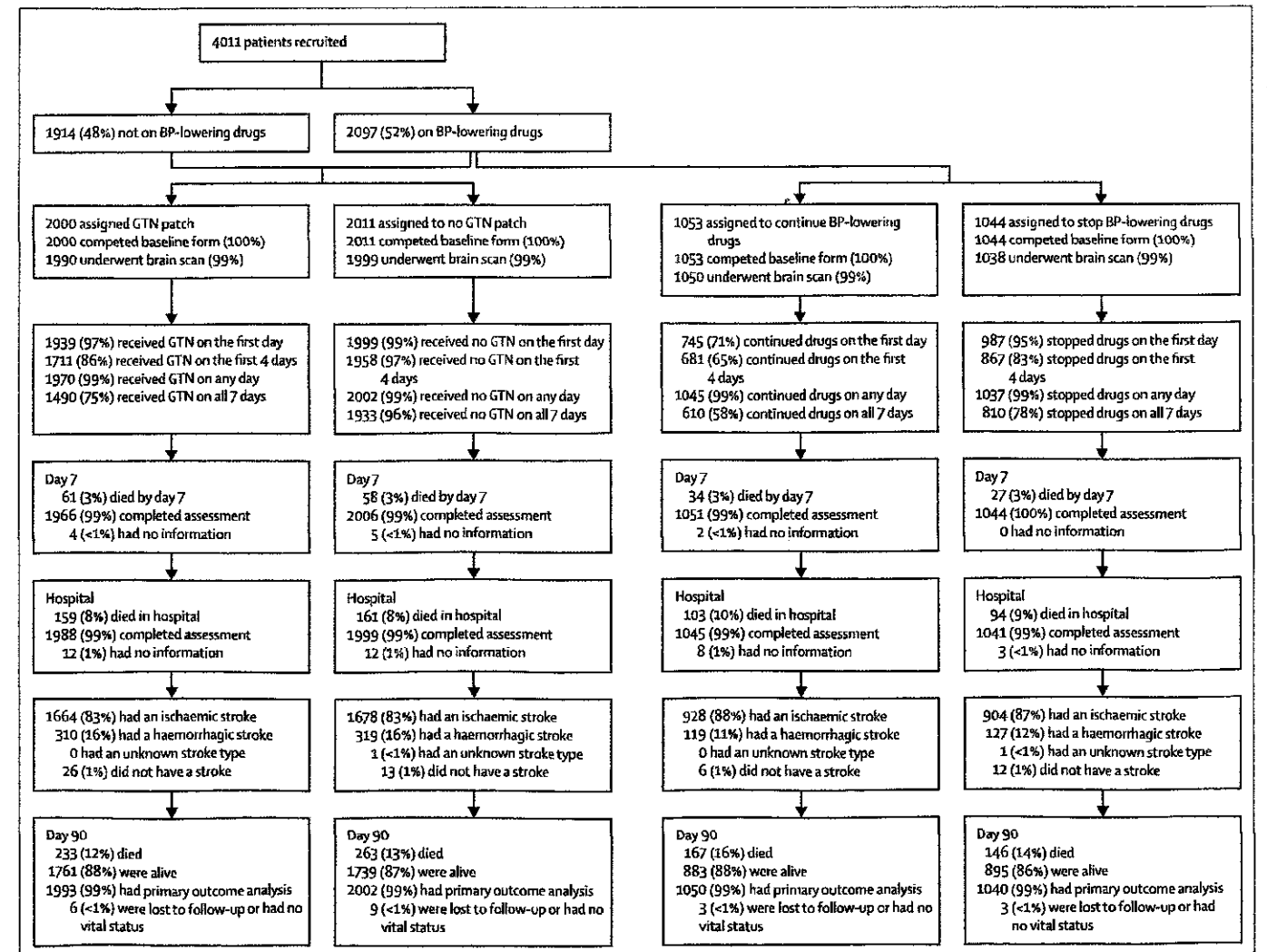


Figure 1: Study profile. Data are n (%). ENOS=efficacy of nitric oxide in stroke. BP=blood pressure. GTN=glyceryl trinitrate.