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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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SUPPLEMENTARY APPENDIX

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Declaration of Interests

The trial was designed, run and funded independently of any manufacturer of glyceryl trinitrate. All authors declare that they have no conflicts of interest.

METHODS

Training of Investigators

All ENOS investigators were trained in the protocol, Good Clinical Practice, and use of the Scandinavian Stroke Scale, modified Rankin Scale (mRS) and Barthel Index. Additionally, outcome assessors were trained in, and then tested with case scenarios, for the mRS.

Schedule for Monitoring of Sites and Data Integrity

Site monitoring was performed by each National Coordinating Centre (NCC) with the aim of ensuring quality control for the delivery of the protocol, collection of data and adherence with national regulations and ethics. Each recruiting site had a start-up visit for training and at least one monitoring visit; further visits were performed as deemed necessary by the NCC. Monitoring visits confirmed the presence of the participant and their consent, eligibility criteria, selected data critical to the trial (demographics, prescription of interventions, and blood pressure), and reported serious adverse events.

Central statistical monitoring of the data was performed according to Buyse *et al* [1] during the trial and prior to locking of the data. Checks included logic and range checks, digit preference, comparison of univariate data between sites, and comparison of multiple variable models between countries. The monitoring procedures were compliant with the requirements of the sponsor, the national ethics committees and regulatory authorities in the participating countries, and fulfilled Good Clinical Practice requirements.

Sample Size Considerations

The trial was originally designed to recruit 5,000 patients so as to detect an absolute risk reduction in the binary outcome of death or dependence (modified Rankin Scale, mRS>2) of 5% from 50% in the control group to 45% in the GTN group (equivalent to odds ratio 0.82), with power 90%, significance 5%, and allowance for losses to follow-up. The original planned method of analysis, as published in the protocol paper,[2] was to compare the proportion of patients who were dead or dependent at 90 days between the treatment groups.

The method for the primary analysis of the mRS was changed when it became clear that binary analysis of the 7-level mRS is sub-optimal and that statistical power is increased by using all the data at each level by comparing differences in distribution across the whole scale between the treatment groups.[3] This approach is now recommended by the European Stroke Organisation.[4] A further, and additional, increase in statistical power is achieved by incorporating key prognostic baseline variables as covariates.[5] Other groups have presented similar findings and used this approach.

The revised statistical analysis plan was based on assessment of the shift in mRS between the treatment groups (GTN/no GTN; continue/stop pre-stroke BP medications), as analysed using ordinal logistic regression, with adjustment for covariates. The overall proposal to change the method of analysis of the primary outcome from binary to ordinal was first presented to, and agreed by, the Trial Steering Committee in January 2008, and confirmed in 2009. An early draft version of this SAP, highlighting this change, was posted on the trial website in April 2009. This change to the design of ENOS was made without knowledge of any interim analysis that split patients by treatment group. The statistician who prepares analyses for the independent Data Monitoring Committee (DMC), and the DMC themselves, were not involved in the writing of this statistical analysis plan (SAP), and have not seen or commented on it.

Data Monitoring Committee (DMC)

The DMC was responsible for safeguarding the interests of trial patients, assessing the

safety and efficacy of the intervention during the trial, assessing data integrity, and for monitoring the overall conduct of the trial. The DMC reviewed the recruitment of patients, and assessed safety and efficacy measures by treatment group. Data were reviewed twice yearly throughout the recruitment period of the trial. The DMC was charged with informing the Trial Steering Committee if, at any time, the data showed evidence beyond reasonable doubt of a difference between the randomised groups in the primary outcome. They also considered these data in the light of external information such as results from completed trials. No formal interim analyses were performed. However, the DMC could perform statistical comparisons as they deemed necessary, with stopping criteria based on the Haybittle-Peto stopping rule (i.e. a difference of 3 standard errors is considered as clear evidence of a treatment effect). The study was not terminated early and the committee did not request any additional analyses of the data.

Inclusion and Exclusion Criteria

Inclusion criteria [2]

a) Adult (age > 18 years).
b) Clinical stroke syndrome with limb weakness lasting at least 1 hour (i.e. not likely to be a transient ischaemic attack).
c) Residual limb weakness at the time of enrolment (SSS Arm <6 and/or Leg <6, appendix C).
d) Onset < 48 hours. If the time of onset is unknown, apply the time when the patient was last known to be well. [This timeframe covers the period of maximum uncertainty over altering blood pressure and should permit the vast majority of otherwise eligible patients to be recruited]
e) Conscious (Glasgow Coma Scale > 8).
f) Systolic blood pressure in range 140 mmHg to 220 mmHg inclusive on the basis of at least one of the three baseline pre-randomisation measures.
g) Independent prior to stroke (pre-morbid modified Rankin Scale < 2).
h) Meaningful consent, or assent from a relative or carer if the patient is unable to give meaningful consent (e.g. in cases of dysphasia, confusion, or reduced conscious level).

Exclusion criteria

a) Definite need for nitrate therapy: e.g. concurrent myocardial infarction, unstable angina, left ventricular failure. Patients admitted on nitrates for the management of stable angina may stop these for the 7 day trial treatment period.
b) Contraindication to nitrate therapy: e.g. hypersensitivity to nitrates, dehydration, hypovolaemia, hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis, marked anaemia, closed-angle glaucoma, sildenafil (Viagra) or related drug, within 24 hours.
c) Definite need for pre-stroke antihypertensive, anti-anginal or anti-heart failure medication: e.g. concurrent angina, heart failure.
d) Definite need for new antihypertensive, anti-anginal or anti-heart failure medication during acute stroke: e.g. concurrent angina, heart failure, hypertensive encephalopathy, aortic dissection.
e) Need for new antihypertensive therapy to lower systolic blood pressure to achieve the enrolment range of 140-220mmHg
f) New (not prescribed pre-stroke) antihypertensive medication commenced after stroke onset
g) Pure sensory stroke.
h) Isolated dysphasia.
i) Patients *expected*, on the basis of existing investigations, to require surgical intervention (e.g. clot evacuation, carotid endarterectomy) during the treatment or follow-up period.
j) *Known* intracerebral pathology other than stroke, e.g. subarachnoid haemorrhage,

brain tumour, cerebral abscess.

k) Other serious condition which is likely to prevent outcome assessment at 90 days, e.g. advanced cancer.
l) Previous enrolment in ENOS.
m) Current involvement in another trial of an experimental drug. [Patients may be randomised into observational studies or non-drug trials.]
n) Not available for follow-up, e.g. no fixed address, overseas visitor.
o) Females of childbearing potential where pregnancy cannot be excluded by a negative pregnancy test, pregnancy, or breastfeeding.

Definition of events

All serious adverse events, as entered into the database by the Site Investigator, were adjudicated by clinical experts who were blinded to treatment assignment. Investigators completed data entry according to the following definitions:[2]

Acute Stroke Unit

A high-dependency nursing unit (or area) caring only/mainly for patients with acute stroke and providing close monitoring of neurological and vascular signs.

Disposition

Home, institution (e.g. warden controlled, nursing home), dead.

Neurological deterioration

A reduction in SSS of > 5 points, or decrease in consciousness level by > 2 points, as compared with baseline.

Recurrent stroke

Classified as haemorrhagic or ischaemic (if documented by CT scan or autopsy), or of unknown type. The time from stroke onset and side will be noted. (This definition deliberately does not attempt to differentiate true recurrence from extension of the presenting lesion since this is clinically and radiologically difficult unless recurrence occurs in a new arterial territory.)

Significant hypotension

A symptomatic fall in blood pressure of > 20% as compared with baseline necessitating intervention with intravenous colloid or crystalloid (saline).

Stroke Rehabilitation Unit

A dedicated rehabilitation unit (or area) caring only/mainly for patients with recent stroke and providing multi-disciplinary therapy (e.g. physiotherapy, occupational therapy, speech & language therapy).

Symptomatic intracranial haemorrhage

Neurological deterioration, or death, associated with significant intracranial haemorrhage found on CT scan or autopsy.

Neuroimaging Scan Adjudication

CT or MRI brain scans were performed according to local site practice at baseline in all patients to confirm the diagnosis. Sites were asked to also perform a follow-up research scan at day 7±1 where patients had provided consent for the additional scan at the time of enrolment. Sites could also perform follow-up scans at any time point after enrolment according to clinical need. The above neuroimages were submitted to the International Coordinating Centre in Nottingham using one of three methods:

a) Sent by courier as a film. Images were then digitised using a Vicom digitiser (VIDAR Diagnostic Pro Advantage, USA).

b) Uploaded onto the trial website as uncompressed encrypted non-anonymised digital DICOM files. Once the trial system had validated the files against the expected patient details, the files were then anonymised.
c) Sent by courier on a CD-ROM or DVD, with files in DICOM format with pseudo-anonymisation of patient details; the patients was identified with their unique study number and initials.

When reviewed, some images were in non-DICOM format (e.g. .PNG, .JPG) and these were converted to DICOM. The anonymised image files, collected as above, were presented to a panel of adjudicators using a browser-based system driven from the trial database. Adjudicators were trained and assessed using the ACCESS system (*www.neuroimage.co.uk/sirs*),[6,7] and reviewed scans blinded to treatment assignment. Adjudication parameters were derived from the IST-3 image adjudication system (J Wardlaw, submitted for publication), and included information on:

a) Presence of an acute stroke lesion: location, mass effect and presence of secondary ischaemia.
b) Presence of pre-stroke changes: atrophy, white matter hyperintensities, old stroke.

Information from adjudication was used to inform the final diagnosis for all patients with a received scan; where clinical and radiological information were incongruent, JMW performed a second adjudication to confirm imaging findings. Patients presenting with an intracerebral haemorrhage had haematoma volume estimated on a visual scale, and measured using the ABC/2 method with presentation of images using OSIRIX (version 3, 32 bit) on an Apple Mac.

Web Table 1. Additional baseline characteristics for patients randomised to continue versus stop pre-stroke antihypertensive drugs.

Characteristic	Continue	Stop
Number of patients	1053	1044
Treated high BP ‡∞	1047 (99.4)	1039 (99.5)
ACE-Inhibitor	533 (50.6)	466 (44.6)
Angiotensin receptor antagonist	157 (14.9)	180 (17.2)
Beta-receptor antagonist	407 (38.7)	413 (39.6)
Calcium channel blocker	343 (32.6)	382 (36.6)
Diuretic	372 (35.3)	363 (34.8)
Alpha-receptor antagonist	78 (7.4)	68 (6.5)
Centrally acting drug	19 (1.8)	13 (1.2)
Other	15 (1.4)	8 (0.8)
No. of BP drugs		
0	6 (0.6)	5 (0.5)
1	454 (43.1)	461 (44.2)
2	371 (35.2)	358 (34.3)
3	164 (15.6)	171 (16.4)
4	52 (4.9)	41 (3.9)
5	5 (0.5)	8 (0.8)
6	1 (0.1)	0 (0)
Median [IQR]	2 [1]	2 [1]
Mean (SD)	1.8 (0.9)	1.8 (0.9)
Fluids and feeding		
Normal diet	424 (40.3)	390 (37.4)
Soft diet	253 (24.0)	256 (24.5)
Nasogastric tube	49 (4.7)	54 (5.2)
Percutaneous feeding tube	4 (0.4)	3 (0.3)
Intravenous/subcutaneous fluids	207 (19.7)	219 (21.0)
No feeding/fluids	116 (11.0)	122 (11.7)

‡ Stratification variable

∞ 11 patients inadvertently entered into continue-stop arm of trial

Web Table 2. Adherence with allocated treatment: glyceryl trinitrate versus no glyceryl trinitrate, and continue versus stop pre-stroke antihypertensive drugs.

Compliance	All	GTN	No GTN	All	Continue	Stop
Number of patients with data	4002	1996	2006	2095	1051	1044
Adherence with first dose	3938 (98.4)	1939 (97.1)	1999 (99.7)	1732 (82.7)	745 (70.9)	987 (94.5)
Adherence during first 4 days	3669 (91.7)	1711 (85.7)	1958 (97.6)	1548 (73.9)	681 (64.8)	867 (83.0)
Adherence during all 7 days	3423 (85.5)	1490 (74.6)	1933 (96.4)	1420 (67.8)	610 (58.0)	810 (77.6)
Non-adherence with all randomised treatment	25 (0.6)	24 (1.2)	1 (0.1)	117 (5.6)	93 (8.8)	24 (2.3)
Reasons for non-adherence by day 4	333 (8.3)	285 (14.3)	48 (2.4)	547 (26.1)	370 (35.2)	177 (17.0)
Discharge before day 4	58 (1.4)	46 (2.3)	12 (0.6)	51 (2.4)	38 (3.6)	13 (1.2)
Adverse event, unacceptable	31 (0.8)	30 (1.5)	1 (0.1)	26 (1.2)	8 (0.8)	18 (1.7)
Headache	13 (0.3)	12 (0.6)	1 (0.1)	6 (0.3)	2 (0.2)	4 (0.4)
Death before day 4	51 (1.3)	32 (1.6)	19 (0.9)	31 (1.5)	15 (1.4)	16 (1.5)
Serious adverse event, non-fatal	28 (0.7)	26 (1.3)	2 (0.1)	29 (1.4)	16 (1.5)	13 (1.2)
Withdrawal of consent	15 (0.4)	14 (0.7)	1 (0.1)	3 (0.1)	1 (0.1)	2 (0.2)
Physician withdrawal	13 (0.3)	12 (0.6)	1 (0.1)	8 (0.4)	1 (0.1)	7 (0.7)
Other reason	137 (3.4)	125 (6.3)	12 (0.6)	399 (19.0)	291 (27.7)	108 (10.3)

Data refer to GTN or any antihypertensives taken during days 1-7, and are number of patients (%). Patients receiving at least first 4 doses are considered to have had complete treatment.

Web Table 3. Blood pressure lowering treatment during the 7 day treatment period: continue versus stop pre-stroke antihypertensive drugs.

	Continue	Stop
Patients with data	1051	1044
Drug class		
Angiotensin converting enzyme inhibitor	516 (49.1)	80 (7.7)
Angiotensin receptor antagonist	162 (15.4)	19 (1.8)
Beta-receptor antagonist	386 (36.7)	92 (8.8)
Calcium channel blocker	336 (32.0)	60 (5.7)
Diuretic	355 (33.8)	65 (6.2)
Alpha receptor antagonist	75 (7.1)	7 (0.7)
Centrally acting drug	13 (1.2)	2 (0.2)
Other	23 (2.2)	12 (1.1)
Number of drugs		
0	63 (6.0)	824 (78.9)
>0	988 (94.0)	220 (21.1)
1	405 (38.5)	142 (13.6)
2	357 (34.0)	46 (4.4)
3	167 (15.9)	27 (2.6)
4	50 (4.8)	3 (0.3)
5	8 (0.8)	2 (0.2)
6	1 (0.1)	0 (0)
Median [IQR]	2 [1]	0 [0]
Mean (SD)	1.8 (1.0)	0.3 (0.7)

Data are based on answers to individual drug classes, and are number (%), median [interquartile range, IQR] or mean (standard deviation, SD).

Web Table 4. Blood pressure (mmHg) at baseline and day 7, by number of antihypertensive drugs at baseline: continue versus stop pre-stroke antihypertensive drugs.

No. drugs	Baseline	Day 7		Difference	2p
		Continue	Stop		
1	166.5 / 88.8	147.5 / 81.7	152.3 / 83.8	-4.8 / -2.1	0.011 / 0.046
2	167.1 / 88.4	143.6 / 78.8	155.2 / 85.9	-11.6 / -7.1	<0.001 / <0.001
3	167.3 / 86.6	145.3 / 78.9	155.8 / 84.9	-10.6 / -6.1	0.001 / 0.002
>3	172.3 / 89.3	143.5 / 78.2	174.0 / 91.5	-30.5 / -13.3	<0.001 / <0.001

Data are mean. Comparison assessed using multiple regression adjusted for baseline.

Web Table 5. Interaction between treatment with GTN versus no GTN, and continue versus stop pre-stroke antihypertensive drugs, for baseline-adjusted systolic and diastolic blood pressure, and heart rate, and absolute mean and median modified Rankin Scale score, across the 6 treatment groups.

GTN	Yes	No	Yes	Yes	No	No	P
Continue	N/A	N/A	Yes	No	Yes	No	
Systolic BP (mmHg)							
Day 1	**-10.7**	-3.1	**-10.7**	**-10.2**	-4.7	-3.2	<0.0001
Day 7	-16.8	-16.2	**-22.5**	-14.1	**-19.4**	-12.3	<0.0001
Diastolic BP (mmHg)							
Day 1	-5.6	-1.7	-4.9	-4.8	-1.7	-1.3	<0.0001
Day 7	**-7.4**	-5.4	**-8.5**	-4.0	**-7.0**	-3.0	<0.0001
Heart rate (bpm)							
Day 1	**1.4**	0.1	0.6	**1.5**	-0.3	0.1	0.004
Day 7	-1.0	-1.1	-0.3	**2.3**	-1.5	**2.8**	<0.0001
mRS (/6)							
Mean	2.9	2.9	3.3	3.2	3.4	3.3	NS
Median	3.0	3.0	3.0	3.0	3.5	3.0	NS

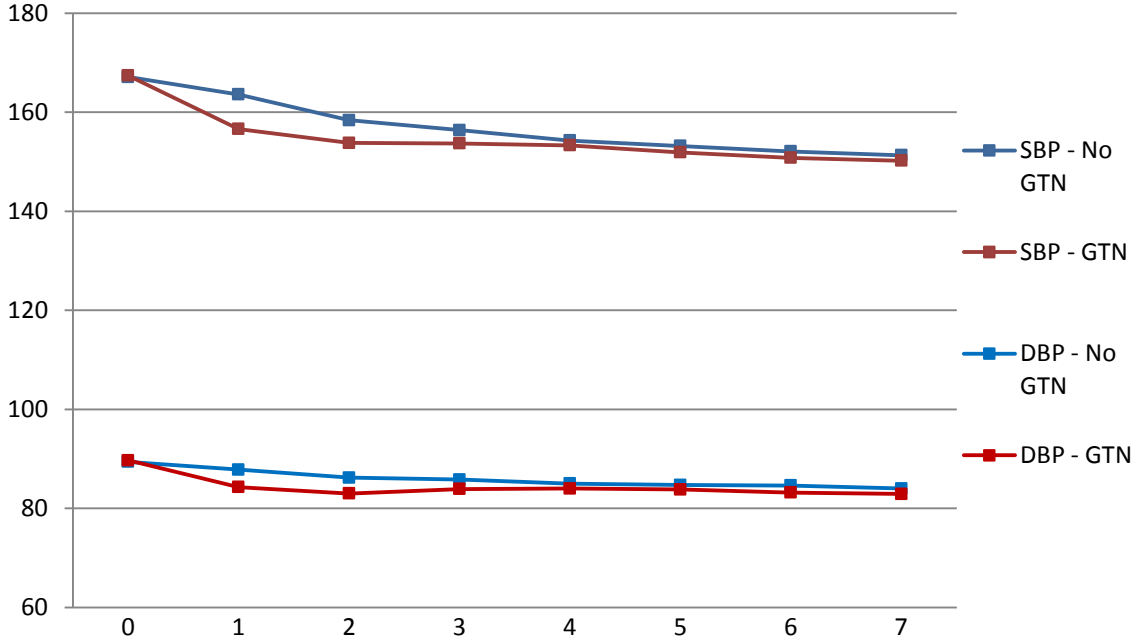
Adjusted data take account of baseline value. Comparisons by Analysis of Variance. Bold identifies largest changes.
Bpm: beats per minute; DBP: diastolic blood pressure; NS: not significant; SBP: systolic blood pressure

Web Table 6. Number of patients with serious adverse events during follow-up to day 90: glyceryl trinitrate versus no glyceryl trinitrate, and continue versus stop pre-stroke antihypertensive drugs.

Cause	All GTN	No GTN	Fatal GTN	No GTN	All Continue	Stop	Fatal Continue	Stop
Complication of initial stroke	40 (2.0)	31 (1.5)	31 (1.6)	28 (1.4)	19 (1.8)	16 (1.5)	16 (1.5)	13 (1.2)
Extension of initial stroke	59 (3.0) †	37 (1.8)	18 (0.9)	11 (0.5)	33 (3.1)	23 (2.2)	13 (1.2)	5 (0.5)
Symptomatic intracranial haemorrhage	59 (3.0)	45 (2.2)	17 (0.9)	16 (0.8)	30 (2.8)	35 (3.4)	8 (0.8)	12 (1.1)
Recurrent stroke	47 (2.4)	35 (1.7)	11 (0.6)	9 (0.4)	25 (2.4)	27 (2.6)	5 (0.5)	8 (0.8)
Myocardial infarction	19 (1.0)	22 (1.1)	7 (0.4)	12 (0.6)	11 (1.0)	16 (1.5)	7 (0.7)	6 (0.6)
Sudden cardiac death	-	-	6 (0.3)	6 (0.3)	-	-	1 (0.1)	5 (0.5)
Other cardiovascular event	118 (5.9)	104 (5.2)	12 (0.6)	14 (0.7)	63 (6.0)	75 (7.2)	10 (0.9)	7 (0.7)
Pulmonary embolism	26 (1.3)	19 (0.9)	6 (0.3)	9 (0.4)	11 (1.0)	13 (1.2)	6 (0.6)	5 (0.5)
Pneumonia	117 (5.9)	122 (6.1)	70 (3.5)	77 (3.8)	88 (8.4) †	63 (6.0)	50 (4.7)	46 (4.4)
Other event	28 (1.4)	28 (1.4)	4 (0.2)	2 (0.1)	13 (1.2)	18 (1.7)	2 (0.2)	2 (0.2)

Data are number of patients (%). Comparison by Chi-square test: † $P \leq 0.05$; all other comparisons are non-significant. Definitions for some events are given above, and in the Statistical Analysis Plan.[8]

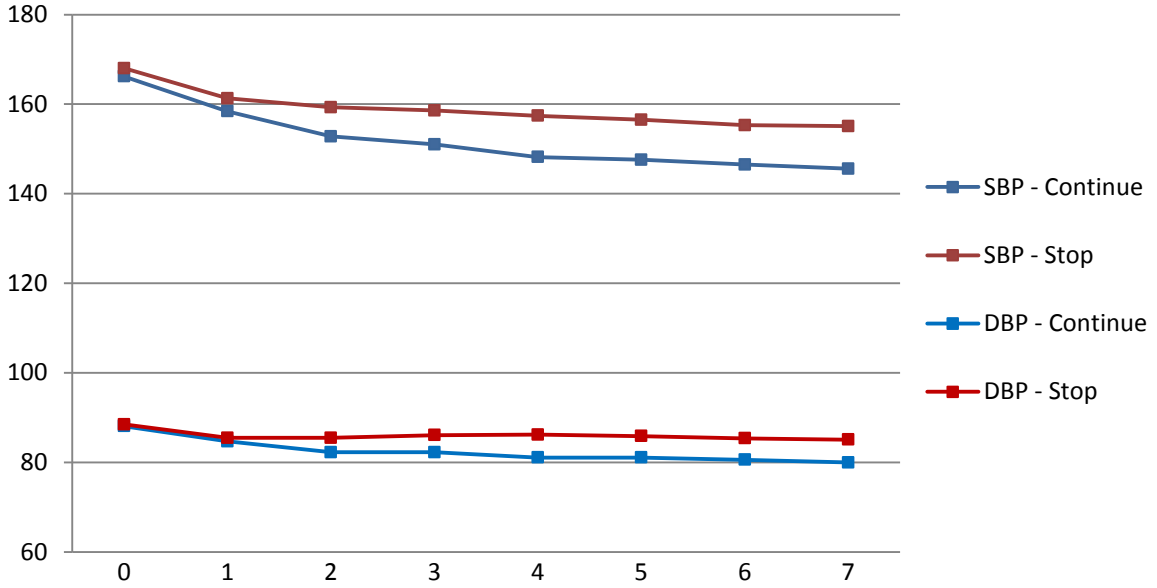
Web Figure 1a. Systolic and diastolic blood pressure over 7 days: glyceryl trinitrate versus no glyceryl trinitrate.



SBP - No GTN	167.1	163.6	158.4	156.4	154.3	153.2	152.1	151.3
SBP - No GTN SD	19.2	22.4	23.2	24.5	24	24.5	24.7	23.6
SBP - GTN	167.4	156.6	153.8	153.7	153.3	151.9	150.8	150.2
SBP - GTN SD	18.7	22.6	24	24.2	24.4	24.5	24.4	24
DBP - No GTN	89.4	87.8	86.2	85.8	85	84.7	84.6	84
DBP - No GTN SD	13.3	14.5	14.8	14.9	14.9	14.7	14.8	14.4
DBP - GTN	89.7	84.3	83	83.9	84	83.8	83.2	82.9
DBP - GTN SD	13	14.1	14.5	14.2	14.4	14.9	14.6	14.7
SBP (MD)	-0.3	7	4.6	2.7	1	1.3	1.3	1.1
DBP (MD)	-0.3	3.5	3.2	1.9	1	0.9	1.4	1.1
SBP 2p	0.83	0.0001	0.0004	0.053	0.5	0.38	0.37	0.45
DBP 2p	0.67	0.0001	0.0001	0.021	0.21	0.33	0.12	0.2

Day 0 is at randomisation; day 1 is 2 hours post-treatment. SBP MD and DBP MD signify mean difference in systolic and diastolic blood pressure between the two treatment groups. Comparisons by independent *t* test at each time point, and repeated measures analysis of variance: $P<0.0001/<0.0001$. Both systolic and diastolic blood pressure had diverged by day two.

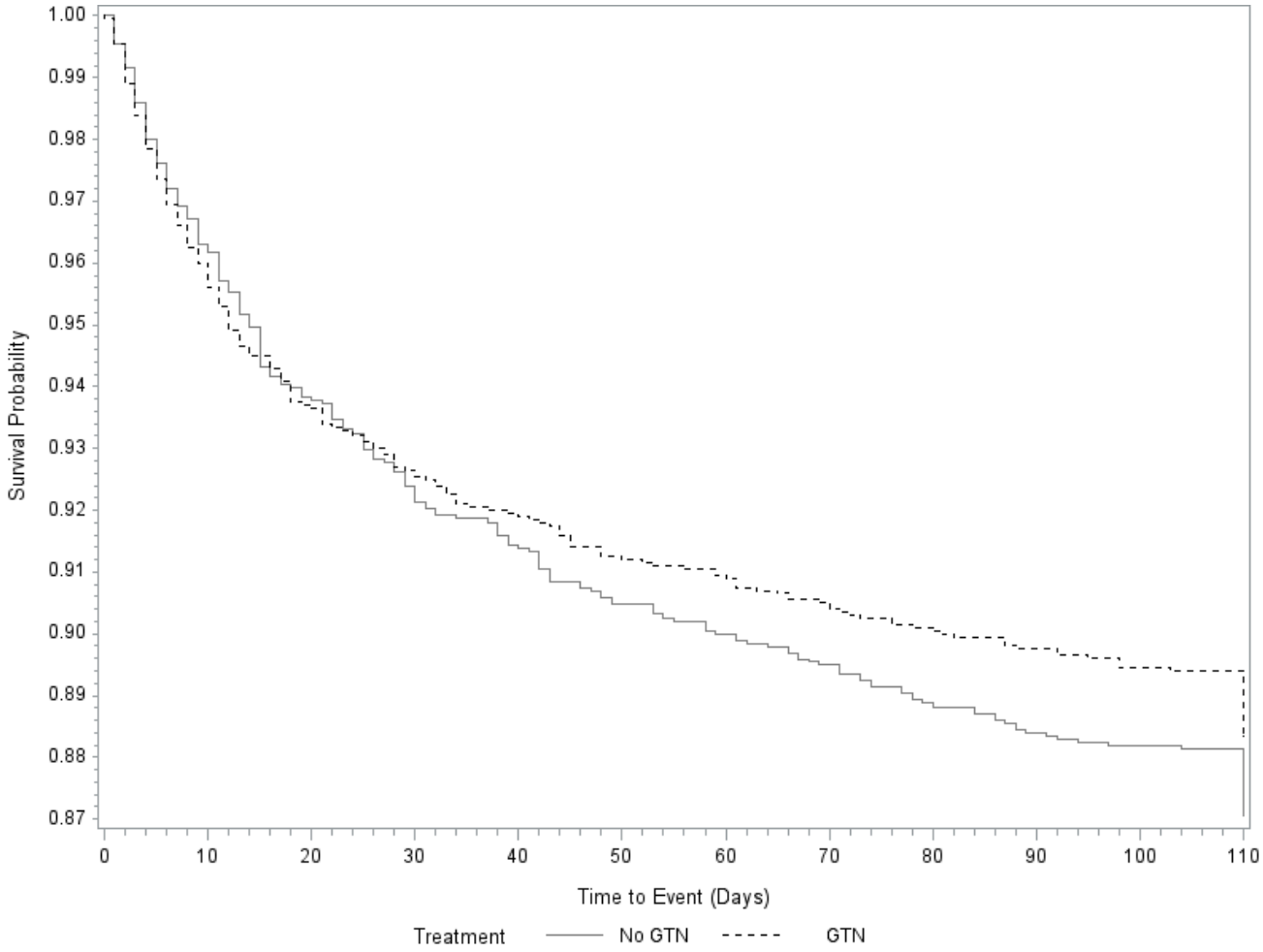
Figure 1b. Systolic and diastolic blood pressure over 7 days: continue versus stop pre-stroke antihypertensive drugs.



	0	1	2	3	4	5	6	7
SBP - Continue	166.2	158.4	152.8	151	148.2	147.6	146.5	145.6
SBP - Continue SD	18.8	22.7	23.8	24.6	24.2	24.3	24.6	24.5
SBP - Stop	168	161.3	159.3	158.6	157.4	156.5	155.3	155.1
SBP - Stop SD	18.7	22.9	23.6	23.6	23.8	24.6	23.4	23.9
DBP - Continue	88.1	84.7	82.3	82.3	81.1	81.1	80.6	80
DBP - Continue SD	13.1	14.2	14.7	14.6	14.4	14.8	14.5	14.7
DBP - Stop	88.5	85.5	85.5	86.1	86.2	85.9	85.4	85.1
DBP - Stop SD	13	14.4	14.7	14.2	14.6	14.5	14.1	14.3
SBP (MD)	-1.8	-2.9	-6.5	-7.6	-9.2	-8.9	-8.8	-9.5
DBP (MD)	-0.4	-0.8	-3.2	-3.8	-5.1	-4.8	-4.8	-5.1
SBP 2p	0.024	0.004	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
DBP 2p	0.45	0.26	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

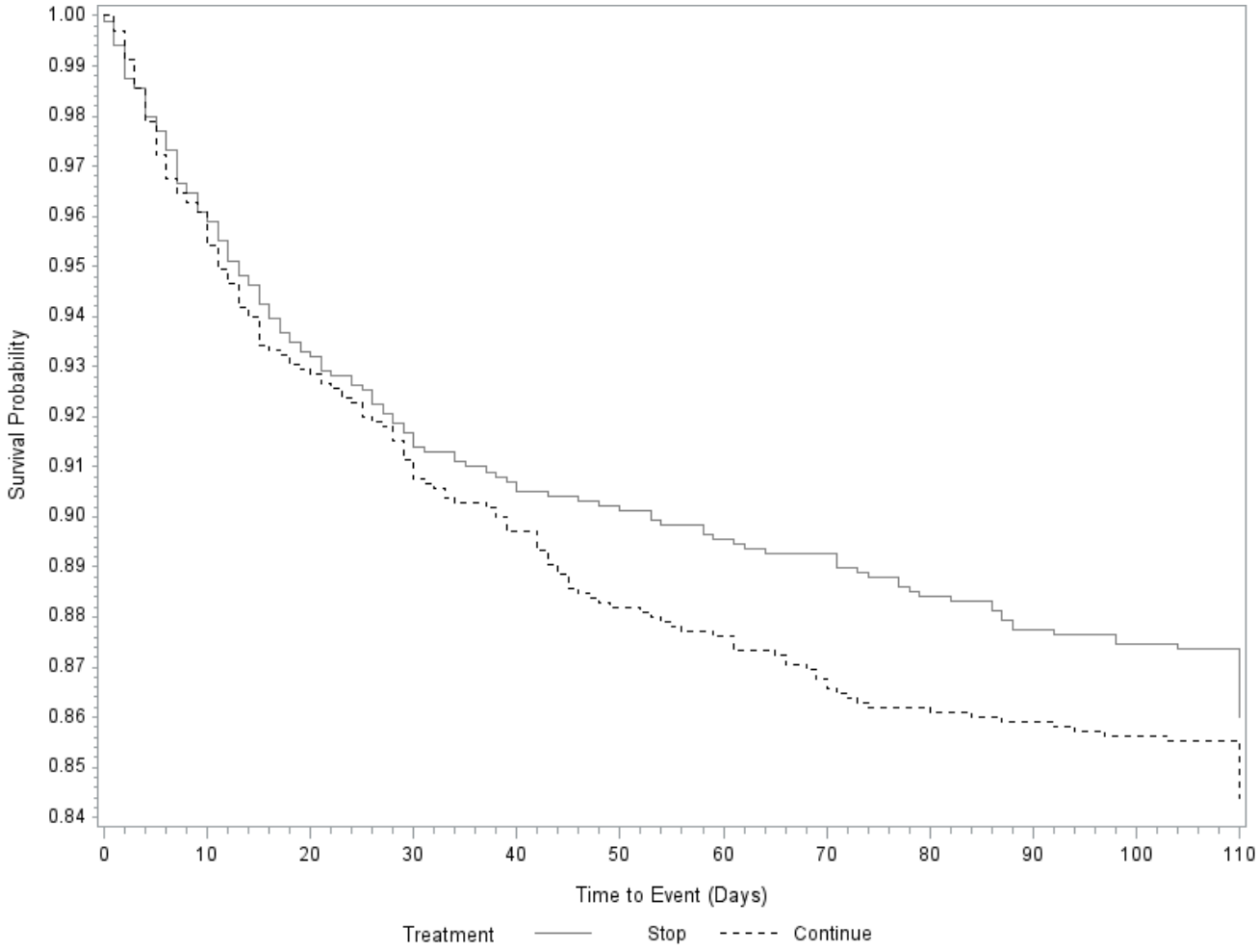
Day 0 is at randomisation; day 1 is 2 hours post-treatment. SBP MD and DBP MD signify mean difference in systolic and diastolic blood pressure between the two treatment groups. Comparisons by independent *t* test at each time point, and repeated measures analysis of variance: $P<0.0001/<0.0001$. Both systolic and diastolic blood pressure had diverged by day two.

Web Figure 2a. Survival curves over the 90 days of follow-up: glyceryl trinitrate versus no glyceryl trinitrate.



Comparison by Cox proportional regression, with adjustment for age, sex, pre-morbid mRS, history of previous stroke, history of diabetes, severity, stroke syndrome (Total Anterior Circulation), stroke type (ischaemic, haemorrhagic, not stroke), systolic blood pressure, alteplase, feeding status, and time to randomisation: hazard ratio=0.93 (95% CI 0.78, 1.12), p=0.44. Date of death was not available for some non-UK patients.

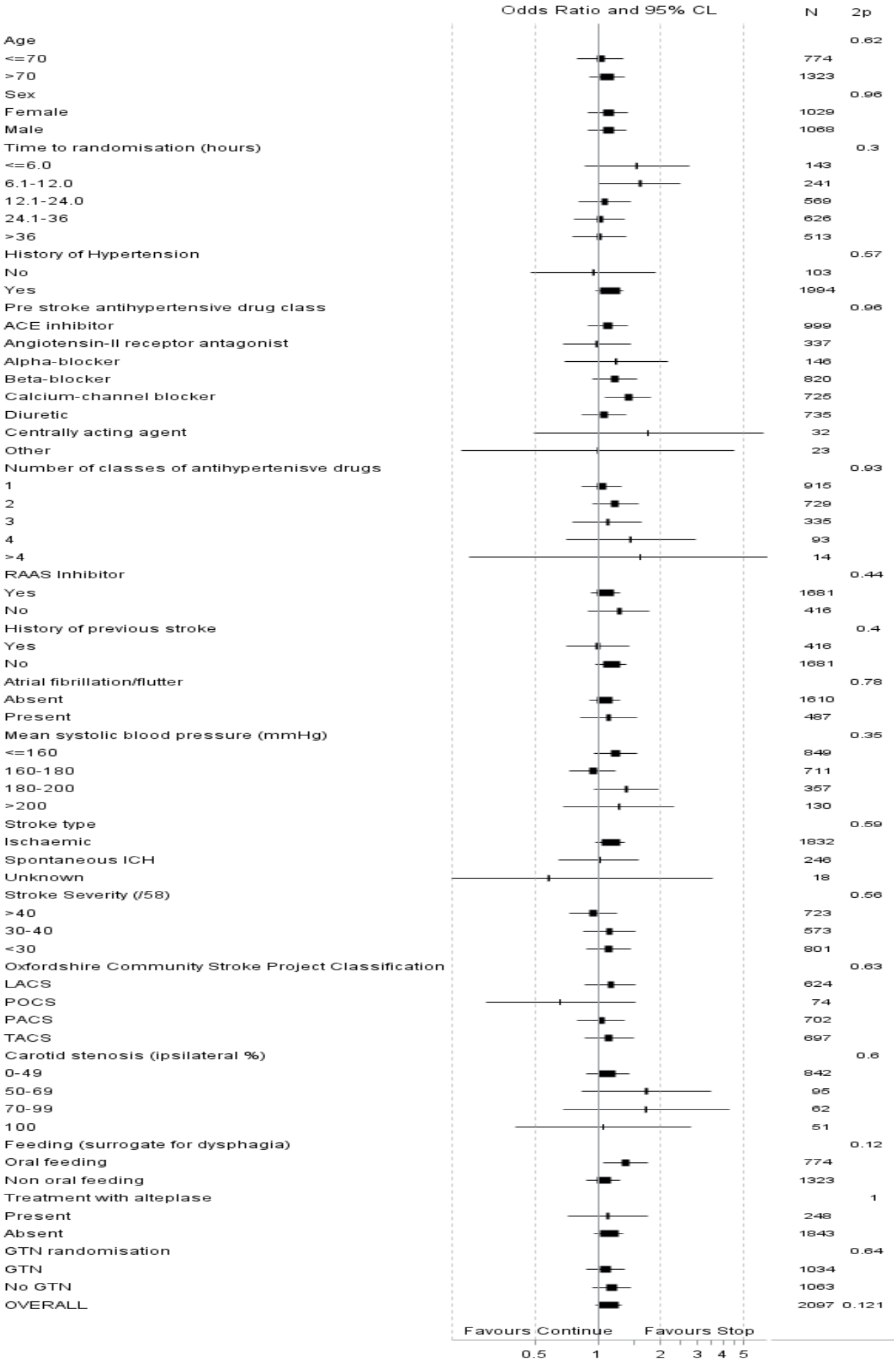
Web Figure 2b. Survival curves over the 90 days of follow-up: continue versus stop pre-stroke antihypertensive drugs.



Comparison by Cox proportional regression, with adjustment for age, sex, pre-morbid mRS, history of previous stroke, history of diabetes, severity, stroke syndrome (Total Anterior Circulation), stroke type (ischaemic, haemorrhagic, not stroke), systolic blood pressure, alteplase, feeding status, and time to randomisation: hazard ratio=1.02 (0.81, 1.27), p=0.88. Date of death was not available for some non-UK patients.

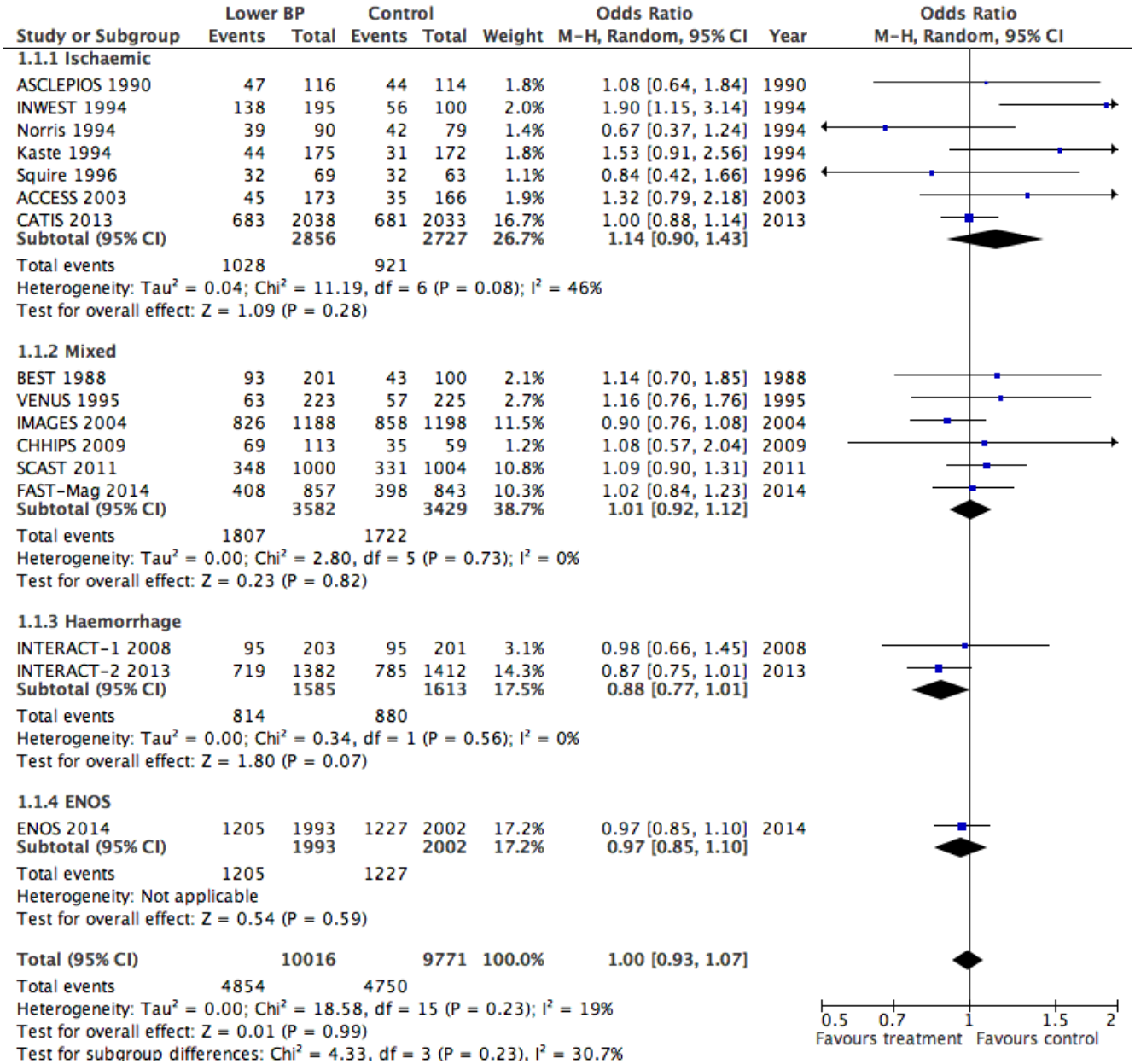
Web Figure 3. Functional outcome in pre-specified subgroups: continue versus stop pre-stroke antihypertensive drugs.

The primary outcome of the study was independence, dependence or death, assessed using the modified Rankin scale (scores of 0, 5 and 6 indicate no symptoms, severe dependency, and death respectively) at 90 days. The black squares represent point estimates for the odds ratio (with the area of the square proportional to the number of events), and the horizontal lines represent 95% confidence intervals. The rectangle incorporates the point estimate and the 95% confidence intervals of the overall effects within categories. P values are for the interaction between subgroup and allocated treatment. Stroke type covers ischaemic stroke, haemorrhagic stroke, stroke of unknown type and non-stroke. Stroke severity is measured using the Scandinavian Stroke Scale (SSS) which ranges from 0 (deep coma) to 58 (normal neurological status). Stroke syndrome is assessed using the Oxfordshire Community Stroke Project: total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), posterior circulation syndrome (POCS) and lacunar syndrome (LACS).


Odds Ratio and 95% CL
N
2p
Age
0.62
<=70
774
>70
1323
Sex
0.96
Female
1029
Male
1068
Time to randomisation (hours)
0.3
<=6.0
143
6.1-12.0
241
12.1-24.0
569
24.1-36
626
>36
513
History of Hypertension
0.57
No
103
Yes
1994
Pre stroke antihypertensive drug class
0.96
ACE inhibitor
999
Angiotensin-II receptor antagonist
337
Alpha-blocker
146
Beta-blocker
820
Calcium-channel blocker
725
Diuretic
735
Centrally acting agent
32
Other
23
Number of classes of antihypertenisve drugs
0.93
1
915
2
729
3
335
4
93
>4
14
RAAS Inhibitor
0.44
Yes
1681
No
416
History of previous stroke
0.4
Yes
416
No
1681
Atrial fibrillation/flutter
0.78
Absent
1610
Present
487
Mean systolic blood pressure (mmHg)
0.35
<=160
849
160-180
711
180-200
357
>200
130
Stroke type
0.59
Ischaemic
1832
Spontaneous ICH
246
Unknown
18
Stroke Severity (/58)
0.56
>40
723
30-40
573
<30
801
Oxfordshire Community Stroke Project Classification
0.63
LACS
624
POCS
74
PACS
702
TACS
697
Carotid stenosis (ipsilateral %)
0.6
0-49
842
50-69
95
70-99
62
100
51
Feeding (surrogate for dysphagia)
0.12
Oral feeding
774
Non oral feeding
1323
Treatment with alteplase
1
Present
248
Absent
1843
GTN randomisation
0.64
GTN
1034
No GTN
1063
OVERALL
2097
0.121
Favours Continue
Favours Stop
0.5
1
2
3
4
5

Web Figure 4a. Meta-analysis of effect of lowering blood pressure on death or dependency (modified Rankin Scale >2). Includes data for glyceryl trinitrate versus no glyceryl trinitrate.

Trials in acute stroke involving drugs which lower blood pressure and which enrolled more than 100 patients. Updated from [9]



Panel: Research in context

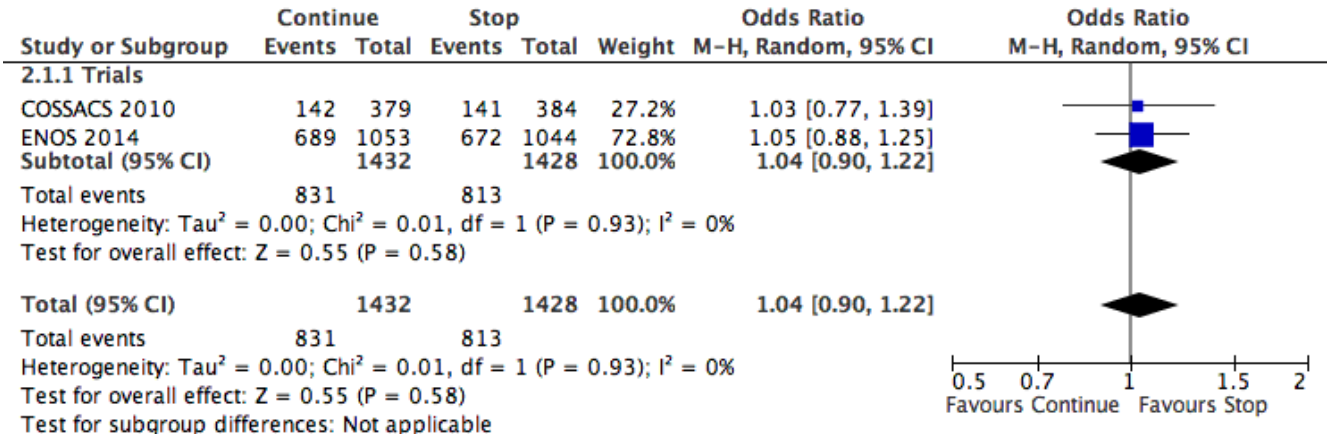
Systematic review

We performed a meta-analysis of randomised controlled trials that compared continuing versus stopping pre-stroke antihypertensive agents in patients with acute stroke. Trials were identified through searches of the Cochrane Library, PubMed and Embase (up to December 2013), and in relevant reference lists. Data were available for 2860 patients for 2 trials (COSSACS [12] and ENOS). Overall, there was no effect of continuing blood pressure treatment (as compared to stopping it temporarily) on functional outcome, odds ratio 1·04 (0·90, 1·22), P=0·58, and no statistical evidence of heterogeneity (chi-square 0·01, P=0·93; I^2 = 0%).

Interpretation

There is no evidence that continuing blood pressure treatment, as compared to stopping it temporarily, improves functional outcome in patients with acute stroke.

Web Figure 4b. Meta-analysis of trials comparing a policy of continuing versus temporary withdrawal of pre-stroke antihypertensive therapy in patients with acute stroke: effect on death or dependency (modified Rankin Scale 3-6).



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