Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Definitions of Ischemic Stroke, Hemorrhagic Stroke, TIA, and Stroke Mimics

1. Diagnosis of stroke

The diagnosis of stroke for trial inclusion was made by history and clinical examination based on the World Health Organization criteria (rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin) (1). The time element was omitted from the definition of stroke for the purposes of trial inclusion. A patient was considered as having a clinical diagnosis of stroke if the above symptoms were present at the time of enrolment. A stroke was defined as acute if the symptoms started no longer than 24 hours before hospital admission. Imaging was not required for trial inclusion.

The final diagnosis of stroke at week one was made by the treating clinician, guided by the above definition including a duration of symptoms of 24 hours or longer and the results of imaging (CT head MRI brain), where available.

2. Definition of an ischemic stroke

An ischemic stroke was defined as a clinical diagnosis of stroke (see 1 above) AND imaging (CT or MRI of the head) that either showed evidence of an acute infarct, was normal, or only showed non-specific changes (e.g. age-associated brain atrophy, small vessel disease, established infarcts in brain areas unrelated to the presenting symptoms).

3. Definition of a hemorrhagic stroke

A hemorrhagic stroke was defined as a clinical diagnosis of stroke AND imaging that showed evidence of an intracerebral hemorrhage.

4. Diagnosis of transient ischemic attack

The diagnosis of transient ischemic attack (TIA) was made by the treating clinician and based on current practice. The UK Clinical Guidelines for Stroke define a transient ischemic attack as ‘a stroke that resolves within 24 hours of onset of symptoms’ (2).

5. Not a stroke

This category included all patients in the study who were found to have non-stroke diagnoses as cause of their presentation with stroke-like symptoms (see 1). These diagnoses would have been made clinically by the treating physician and /or by imaging and included: migraine, epileptic seizure, brain tumor, functional stroke, cervical spondylosis. No specific definitions were given to guide diagnosis.

References

1. Aho K, Harmsen P, Hatano S, et al. Cerebrovascular disease in the community: Results of a WHO collaborative study. *Bull World Health Organ* 1980;**58**:113-130.

2. The Intercollegiate Stroke Working Party. National clinical guideline for stroke. 5th edition. Royal College of Physicians, London 2016 (section 1.4).

eTable 1. Informed Consent

	Continuous oxygen (n=2668)	Nocturnal oxygen (n=2667)	Control (n=2668)
Consent given by the patient; *n* (%)	2329 (87%)	2340 (88%)	2322 (87%)
Consent given by a relative, carer, or independent legal representative; *n* (%)	339 (13%)	327 (12%)	346 (13%)
Withdrawal from the trial 0-7 days (total); *n* (%)	16 (0.6%)	20 (0.7%)	4 (0.15%)
Patients who gave the initial consent themselves; n (%)	14 (0.5%)	17 (0.6%)	3 (0.11%)
Patients who were included by a relative, carer, or legal representative; n (%)	2 (0.1%)	3 (0.1%)	1 (0.04%)
Withdrawal from the trial 0-90 days (total); *n* (%)	56 (2.1%)	63 (2.4%)	57 (2.1%)
Patients who gave the initial consent themselves; n (%)	48 (1.8%)	56 (2.1%)	44 (1.6%)
Patients who were included by a relative, carer, or legal representative; n (%)	8 (0.3%)	7 (0.3%)	13 (0.5%)

Patients who were incompetent to give fully informed consent at randomization and were enrolled with consent from a relative, carer or independent legal representative were asked to confirm consent once competence was regained. This was documented for all participants at one week.

eTable 2. Adherence to the Trial Intervention

	Continuous oxygen (*n*=2668)	**Nocturnal oxygen (*n*=2667)**	**Control (*n*=2668)**
Trial oxygen prescribed in the drug chart for 72h / 3 nights and signed for each dose; *n* (%)	1369 (51%)	1426 (53%)	21 (0·9%)
Trial oxygen prescribed in the drug chart for 72h / 3 nights but not signed for every time point; *n* (%)	789 (30%)	799 (30%)	2 (0·1%)
Trial oxygen stopped before 72 hours; *n* (%)	433 (16%)	361 (14%)	10 (0·4%)
No trial oxygen prescribed; *n* (%)	4 (0·2%)	10 (0·4%)	2229 (83.5%)
No data; *n* (%)	73 (2.8%)	71 (2.6%)	406 (15.2%)

Oxygen was prescribed as randomized in 2591 participants in the continuous oxygen group and in 2586 participants in the nocturnal oxygen group. The most common reason for stopping oxygen treatment before the end of the intervention period was discharge from hospital. In day-to-day clinical practice, oxygen is given continuously and prescribed at the start of treatment and re-prescribed if the dose changes, with no nurse signatures for administration. For the purposes of this trial we asked nurses to sign oxygen treatment at each drug round. This was an unusual procedure for ward staff, and not always followed. Most of the patients where oxygen was prescribed, but not signed would have been given oxygen, as prescribed.

eTable 3. Sensitivity Analyses (Unadjusted Except Where Specified Otherwise)

	Odds ratio (95% confidence interval); *p* value	
	Oxygen vs no oxygen[a]	**Continuous vs nocturnal[b]**
Complete case analysis	0.970 (0.892, 1.054); 0.471	1.025 (0.931, 1.129); 0.611
Multiple imputation analysis[c]	0.974 (0.895, 1.061); 0.549	1.031 (0.933, 1.135); 0.530
Best-case imputation[d]	1.178 (1.085, 1.279); <0.001	1.221 (1.111, 1.342); <0.001
Worst-case imputation[e]	0.803 (0.740, 0.872); <0.001	0.862 (0.784, 0.947); 0.002
Adherers only[f]	0.947 (0.851, 1.054); 0.317	1.035 (0.895, 1.196); 0.645

[a] Reference category is 'no oxygen'; outcome is a one-point lower (better) score on mRS.

[b] Reference category is 'nocturnal'; outcome is a one-point lower (better) score on mRS.

[c] Based on 20 imputed datasets, using chained equations. The imputation variables were: age, sex, treatment group, baseline oxygen saturation, baseline 'six simple variables' prognostic index for 6-month independence, baseline National Institutes of Health Stroke Scale score, and values of the mRS at other time points.

[d] Missing values for 'oxygen' and 'continuous' are given good score (0 or 1), missing cases for 'no oxygen' and 'nocturnal' are given poor score (5 or 6); confidence intervals and *p* values have been adjusted for the imputation.

[e] Missing values for 'oxygen' and 'continuous' are given poor score (5 or 6), missing cases for 'no oxygen' and 'nocturnal' are given good score (0 or 1); confidence intervals and *p* values have been adjusted for the imputation.

[f] Adherers only (trial oxygen prescribed and signed as given or no trial oxygen given for controls and correct dose of oxygen given and no oxygen given for clinical indications and modified Rankin Scale score not missing at 90 days: n=2350 for combined oxygen (continuous oxygen n=1101 and nocturnal oxygen n=1249) and n=1994 for control. Analysis adjusted for age, sex, baseline NIHSS score, baseline oxygen saturation, and 'six simple variables' prognostic index for 6-month independence, to account for loss of equivalence from randomization.

Findings of the sensitivity analysis for imputed data and adherers only were very similar to the main analysis. The best- and worst-case imputations indicate the plausible maximum bounds of any potential bias from missing data, and produced more extreme, statistically significant differences.

eTable 4. Secondary, Exploratory, and Safety Outcomes—Adjusted Analyses

	n *N*=8003	Comparison 1 Oxygen vs. Control		Comparison 2 Continuous vs. Nocturnal	
		OR or MD (99%CI)	p-value	OR or MD (99%CI)	p-value
Secondary outcomes at 72 hours					
Highest oxygen saturation	7860	MD 0·70 (0.62, 0.78)	<0·001[a]	MD 0·31 (0.22, 0.40)	<0·001[a]
Lowest oxygen saturation	7860	MD 0·64 (0.50, 0.77)	<0·001[a]	MD 0·47 (0.32, 0.62)	<0·001[a]
Oxygen saturation <90%	7860	OR 0.46 (0.29, 0.71)	<0·001[b]	OR 1.32 (0.70, 2.48)	0·27[b]
Oxygen saturation <95%	7860	OR 0.67 (0.49, 0.91)	<0·001[b]	OR 0.62 (0.43, 0.90)	0·27[b]
Need for additional oxygen	7809	OR 1.36 (1.07, 1.73)	0·001[b]	OR 1.23 (0.96, 1.59)	0·001[b]
Secondary outcomes at 7 days					
NIHSS	7778	MD -0.10 (-0.35, 0.15)	0·28[a]	MD 0.08 (-0.20, 0.37)	0·45[a]
Neurological improvement	7778	OR 0·98 (0·86, 1·11)	0·63[b]	OR 0·97 (0·84, 1·13)	0·63[b]
Death by 7 days	7959	OR 0.93 (0.57, 1.52)	0·71[b]	OR 1.40 (0.78, 2.52)	0·14[b]
Secondary outcomes at 90 days					
Death by 90 days	7677	OR 1.03 (0.81,1.30)	0.79[b]	OR 1.09 (0.83,1.43)	0·42[b]
Alive and independent (mRS≤2)	7677	OR 0·96 (0·83, 1.11)	0·45[b]	OR 1·02 (0.87, 1.20)	0·74[b]
Living at home	6859	OR 0·98 (0·80, 1.19)	0·76[b]	OR 1·06 (0.84, 1.33)	0·53[b]
Barthel ADL index (out of 100)	6549	MD -0·03 (-1.94, 1.88)	0·97[a]	MD -0·01 (-2.24, 2.21)	0·99[a]
Nottingham Extended ADL (0–21)	7528	MD -0·15 (-0.51, 0.21)	0·30[a]	MD 0·18 (-0.24, 0.60)	0·27[a]
Quality of Life (EQ5D-3L) (-0.59-1)	7248	MD 0·00 (-0.02, 0.03)	0·57[a]	MD 0·01 (-0.02, 0.03)	0·55[a]
Quality of Life (VAS) (0–100)	6675	MD 0·34 (-1.44, 2.11)	0.63[a]	MD 0·05 (-2.01, 2.10)	0.95[a]
Exploratory Outcomes					
Highest HR during the intervention	7859	MD -0.11 (-1.09, 0.86)	-	MD -0.88 (-2.03, 0.26)	-
Highest sBP during the intervention	7864	MD -2.06 (-3.52,-0.59)	-	MD -0.33 (-2.03, 1.37)	-
Highest dBP during the intervention	7861	MD -1.12 (-2.06, -0.17)	-	MD -0.79 (-1.87, 0.30)	-
Highest temperature within 7days	7877	MD 0.00 (-0.03, 0.04)	-	MD -0.01 (-0.05, 0.03)	-
Antibiotics given within 7days	7916	OR 0.99 (0.83, 1.19)	-	OR 1.02 (0.83, 1.26)	-
Sedatives given within 7days	7916	OR 0.98 (0.75, 1.28)	-	OR 0.85 (0.63, 1.16)	-
Sleep as good as before the stroke	6584	OR 0·98 (0·85, 1·13)	-	OR 0·96 (0.81, 1.13)	-
No significant speech problems	6716	OR 1·08 (0·88, 1·34)	-	OR 1·06 (0·83, 1·36)	-
Memory as good as before the stroke	6646	OR 1.02 (0.89, 1.17)	-	OR 0.96 (0.82, 1.13)	-
Safety					
Serious adverse events (SAEs)	8003	RR 0.94 (0.82, 1.08)	0·40[c]	RR 1.19 (1.02, 1.39)	0·03[c]
Participants with at least one SAE	8003	OR 0.99 (0.82, 1.21)	0·93[b]	OR 1·21 (0.97, 1.52)	0·03[b]

Significance testing was by multivariable linear regression[a] or multivariable logistic regression[b] or multivariable negative binomial regression.[c] Adjusted mean differences (MD) are reported for means, adjusted odds ratios (OR) for frequencies, and adjusted rate ratios (RR) for count data. The following variables were used for the adjusted analysis: age, sex, baseline NIHSS score, baseline oxygen saturation, and the 'six simple variables' prognostic index. ORs >1 indicate that the outcome is more likely with oxygen than with control (reference category) in comparison 1 and more likely with continuous oxygen than with nocturnal oxygen (reference category) in comparison 2. Neurological improvement is a decrease of 4 or more or to zero on the National Institutes of Health Stroke Scale (NIHSS). Alive and independent is a modified Rankin Scale score of 2 or less. As outlined in the statistical analysis plan we have not conducted significance tests on the exploratory data and the outcomes suggested by patients and carers. Activities of daily living (ADL), quality of life (EQ5D-3L), visual analogue scale (VAS), heart rate (HR), systolic blood pressure (sBP), diastolic blood pressure (dBP).

eTable 5. Total Number of Serious Adverse Events by Event Categories

	Continuous oxygen (*n*=2668)	Nocturnal oxygen (*n*=2667)	Control (*n*=2668)	**Total** (*n*=8003)
Cardiovascular	54	48	37	139
Deep vein thrombosis	4	3	3	10
Pulmonary embolism	18	6	9	33
Central nervous system	177	141	178	496
Agitation	*3*	*0*	*0*	*3*
Anxiety	*1*	*1*	*2*	*4*
Central nervous system other	*3*	*5*	*2*	*10*
Cerebral edema	*10*	*2*	*6*	*18*
Complication of initial stroke	*36*	*26*	*23*	*85*
Confusion	*2*	*3*	*0*	*5*
Dementia	*0*	*0*	*2*	*2*
Extension of initial stroke	*34*	*32*	*45*	*111*
Functional symptoms	*0*	*2*	*0*	*2*
Hemorrhagic transformation	*8*	*8*	*16*	*32*
Headache	*1*	*3*	*2*	*6*
Intracerebral bleed	*12*	*8*	*4*	*24*
Intracranial/extracerebral bleed	*1*	*1*	*4*	*6*
Recurrent stroke	*41*	*36*	*42*	*119*
Seizure	*10*	*7*	*18*	*35*
Transient ischemic attack	*13*	*7*	*10*	*30*
Vertigo	*1*	*0*	*0*	*1*
Vomiting	*1*	*0*	*2*	*3*
Cutaneous	1	0	0	1
Gastro-intestinal	15	9	13	37
Genito-urinary	11	10	21	42
Hematological	0	1	0	1
Immunological	0	0	0	0
Miscellaneous	40	33	37	110
Respiratory	76	84	97	257
Chest infection	*2*	*4*	*3*	*9*
Hypoxia	*3*	*1*	*6*	*10*
Pneumonia	*69*	*78*	*87*	*234*
Respiratory other	*2*	*1*	*1*	*4*
Oxygen-related	0	0	0	0
Drying of mucous membranes	*0*	*0*	*0*	*0*
Respiratory depression	*0*	*0*	*0*	*0*
Other	30	23	23	76
Total	426	358	418	1202

This table gives the total number and categories of serious adverse events (SAEs) reported up to 90 days after randomization. Figures indented and in italics are data for subcategories. Functional symptoms are symptoms that are not explained by underlying physical disease.