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TITLE PAGE

Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke: the Stroke Oxygen Study randomized clinical trial

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KEY POINTS

Question: Does routine prophylactic low-dose oxygen supplementation after acute stroke improve functional outcome?

Findings: In this randomized clinical trial 8003 patients with acute stroke were allocated within 24 hours of admission to 3 days of continuous oxygen, nocturnal oxygen, or control. After 3 months there was no significant difference in death and disability for the combined oxygen groups compared with control (odds ratio 0.97), or for continuous oxygen compared with nocturnal oxygen (odds ratio 1.03).

Meaning: Routine low-dose oxygen did not improve outcomes in non-hypoxic patients after acute stroke.

ABSTRACT

Importance: Hypoxia is common in the first few days after acute stroke, frequently intermittent, and often undetected. Oxygen supplementation could prevent hypoxia and secondary neurological deterioration and thus has the potential to improve recovery.

Objective: To assess whether routine prophylactic low-dose oxygen therapy is superior to control in reducing death and disability at 90 days and, if so, whether oxygen given at night only, when hypoxia is most frequent, and oxygen administration is least likely to interfere with rehabilitation, is more effective than continuous supplementation.

Design, setting, and participants: In this single-blind randomized clinical trial 8003 adults with acute stroke were enrolled from 136 participating centers within 24 hours of hospital admission, if they had no clear indications for, or contraindications to, oxygen treatment (first patient enrolled 24-Apr-2008, last follow-up 27-Jan-2015).

Interventions: Participants were randomized 1:1:1 to continuous oxygen for 72 hours (n=2668), nocturnal (21:00-07:00) oxygen for three nights (n=2667), or control (oxygen only if clinically indicated, n=2668). Oxygen was given via nasal tubes at 3L/min if baseline oxygen saturation was ≤93% and at 2L/min if >93%.

Main outcomes and measures: The primary outcome was the modified Rankin Scale (mRS) score (a measure of disability ranging from 0=no symptoms to 6=death, minimum clinically important difference 1 point), assessed at 90 days by postal questionnaire (participant aware, assessor blinded). The mRS was analyzed by ordinal logistic regression, which yields a 'common' odds ratio (OR) for a change from one disability level to the next better (lower) level; OR > 1.00 indicates improvement. Significance was set at $p \leq 0.05$ for the primary outcomes and ≤ 0.01 for all other outcomes.

Results: 8003 patients (4398 (55%) males, mean age 72 (SD13) years; median NIHSS 5; mean baseline oxygen saturation 96.6%) were enrolled. The primary outcome was available in 7677 (96%) participants. The unadjusted odds ratio for a better outcome (calculated via ordinal logistic regression) was 0.97 (95% CI 0.89–1.05), p=0.47 for oxygen versus control, and 1.03 (95% CI 0.93–1.13), p=0.61 for continuous versus nocturnal oxygen. No subgroup could be identified that benefited from oxygen. There were 348 (13.0%), 294 (11.0%), and 322 (12.1%) participants with at least one serious adverse event in the continuous, nocturnal, and control groups respectively. No significant harms were identified.

Conclusions and relevance: Among non-hypoxic patients with acute stroke the prophylactic use of low-dose oxygen supplementation did not reduce death or disability at 3 months. These findings do not support low-dose oxygen in this setting.

Trial Registration: ISRCTN52416964

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INTRODUCTION

Hypoxia is common during the first days after an acute stroke,[1] and associated with higher rates of neurological deterioration,[2] death and institutionalization,[3] and greater mortality.[4] While cells in the ischemic penumbra are only viable for a few hours, brain cells beyond the ischemic core and penumbra remain at risk of delayed cell death for several days owing to vasogenic edema, inflammation, and programmed cell death, particularly if metabolic disturbances are compounded by hypoxia.[5,6,7] Continuous monitoring is associated with better outcomes,[8] but even in intensively monitored patients, hypoxia is not always identified and treated. Adverse outcomes were observed to be increased when only some desaturations <90% were treated with oxygen, and reduced when all were treated.[3]

Supplemental oxygen could improve outcomes by preventing hypoxia and secondary brain damage, but could also have adverse effects.[9] These include vasoconstriction and pulmonary toxicity with high concentrations,[9] respiratory tract infection due to contamination of the giving set, the tubing acting as an impediment to mobilization, stress, and the direct effects of oxygen on vascular tone and blood pressure.[10] Three small trials of short-term (≤12 hours), high-flow (10-45 L/min) therapeutic oxygen, aimed at generating supra-physiological blood oxygen levels, have not shown improved outcomes. [11, 12, 13] A larger trial (n=550) using low-dose supplemental oxygen (3 L/min for 24 hours) also showed no benefit,[14] but early neurological recovery was improved in a study giving low-dose oxygen over 72 hours.[15]

The primary aim of the Stroke Oxygen Study (SO_2S) was to determine whether low-dose oxygen therapy during the first 3 days after an acute stroke improves outcome compared to usual care (oxygen only when needed). As oxygen may restrict mobility and interfere with daytime activities, the secondary hypothesis was that oxygen given at night only, when hypoxia is most likely, is more effective than continuous oxygen supplementation.

METHODS

Study design

This was a multi-center randomized clinical trial of oxygen supplementation with single-blind outcome assessment. The protocol (see online supplement),[16] statistical analysis plan (see online supplement),[17] and data collection forms[18] are published. Fully informed written or witnessed oral consent was given by the participants or, if they did not have capacity to consent, by a legal representative. The protocol was approved by the North Staffordshire Research Ethics Committee (06/Q2604/109).

Participants

Adults (≥18 years) with a clinical diagnosis of acute stroke (see eText 1 for definition) within 24 h of hospital admission, who had no clinical indications for, or contraindications to, oxygen treatment, or any concomitant condition likely to limit life expectancy to <12 months were eligible.

Randomization and interventions

Participants were allocated 1:1:1 via central web-based minimized randomization[19] to one of three groups: i) continuous oxygen supplementation, ii) nocturnal oxygen supplementation only, iii) no routine oxygen (control). The factors for which imbalances were minimized were: the 'six simple variables' (SSV) prognostic index for independent survival at 6 months[20] (cut-offs ≤0.1, >0.1 to ≤0.35, >0.35 to ≤0.70, >0.70), oxygen treatment before randomization (yes, no, unknown), baseline oxygen saturation on air (<95, ≥95%), and time since stroke onset (defined as the last time well for wake-up strokes) (≤3, >3 to ≤6, >6 to ≤12, >12 to ≤24, >24 hours). No blocking was used. Oxygen was administered per nasal tubes either continuously (day and night) during the first 72 h after randomization or overnight (21:00–07:00) for three nights. Oxygen was given at a flow rate of 3

L/min if baseline saturation was 93% or below, or at a flow rate of 2 L/min, if baseline saturation was greater than 93%. In the control group no routine oxygen supplementation was given. Vital signs were observed at least 6-hourly, with any abnormal findings treated independently of trial allocation. Patients requiring oxygen in the control group, or in the nocturnal oxygen group during the day, or needing changes in oxygen dosage for clinical reasons, were given the appropriate concentration of oxygen irrespective of treatment group. In addition, for 4144 patients recruited in the latter half of the study, spot checks of treatment adherence were undertaken at midnight and 6 am.

Outcomes and blinding

Outcomes were assessed at one week by a member of the local research team and at 90 days via postal questionnaire. Telephone interviews were conducted with non-responders, or to clarify unclear or missing answers. The primary outcome was the modified Rankin Scale (mRS) [21] score (a measure of disability ranging from 0=no symptoms to 6=death; minimum clinically important difference 1 point) at 90 days. Secondary outcomes were: number of participants with neurological improvement, defined as a ≥4-point decrease on the National Institutes of Health Stroke Scale (NIHSS)[22, 23] between randomization and day 7, the highest and lowest oxygen saturations within the first 72 h, and mortality at one week. Further secondary outcomes at 90 days were: mortality, number of participants alive and independent (mRS≤2), number of participants living at home, Barthel Index (BI) activities of daily living (ADL) score,[24] quality of life (EuroQol EQ5D-3L),[25] and Nottingham Extended Activities of Daily Living (NEADL) score.[26] For the NIHSS and BI, deaths were recorded as the worst outcome on the scale.[27] Participants, their doctors, and local research staff who recorded the one-week outcomes were not blind to the study interventions. 90-day assessments were undertaken by the SO_2S study office blind to treatment allocation.

Study size

The initial recruitment target was 6,000 participants, which was estimated to provide 90% power to detect small (0.2 mRS-point, e.g. a one-point improvement in one in 5 participants) differences between oxygen (continuous and night only groups combined) and no oxygen at $p \leq 0.01$, and 90% power at $p \leq 0.05$ to detect small differences between continuous oxygen and oxygen at night only. The study size was subsequently revised to 8,000 participants, using ordinal methods,[16,17] without knowledge of interim results, to increase the number of patients with severe strokes and thereby provide greater power to investigate any differential effectiveness of oxygen versus control within subgroups (defined by severity).

Statistical analysis

The trial was designed to answer two key questions: firstly, whether oxygen supplementation improves outcome (mRS at 90 days) and secondly, whether giving oxygen at night is more effective than giving it continuously. The main comparisons therefore were of the two combined oxygen groups (continuous and night-time only) versus control, and of continuous oxygen versus oxygen at night only. The statistical analysis plan describes the analysis methods in detail (see online supplement).[17]

The mRS was analysed by ordinal logistic regression, which yields a 'common' odds ratio (OR) for a move from one level to the next better (lower) level with an odds ratio more than 1.00 indicating an improvement. For this and other outcome variables, a primary unadjusted analysis and a secondary covariate-adjusted analysis were performed. Adjusted analyses incorporated the following covariates: age, sex, baseline NIHSS score, baseline oxygen saturation, and the SSV prognostic index for 6-month independence (or for analysis of mortality, the SSV prognostic index for 30-day survival). Sensitivity analysis for the mRS used multiple imputation of missing values (using a chained equations method, with 20 imputed datasets). Additional imputations were performed to allow for the possibility that data were missing not at random and were either i) better or ii) worse than expected; missing values were thereby replaced by either very good (i.e. lowest) or very poor (i.e. highest) scores on the mRS, as appropriate (see eTable 3 in supplementary appendix). Subgroups, for the mRS only, were analysed by an interaction term, and were predefined in the statistical analysis plan[17] (see figure 2 for details of subgroups).

For continuous outcomes, means and standard deviations (SD) or medians and interquartile ranges (IQR) are reported, as appropriate. Unadjusted analyses used unrelated t-tests, with the mean difference between treatments and corresponding confidence interval (CI) reported. The adjusted analysis used analysis of covariance, with the covariates specified earlier included in the analysis.

For dichotomous outcomes, percentages were compared across the treatment comparisons using a chi-squared test (unadjusted analyses). Adjusted analyses of dichotomous outcomes used binary logistic regression, with the covariates listed earlier; ORs and confidence intervals are reported.

All analyses were by intention to treat, i.e. according to the treatment group to which participants were allocated, irrespective of treatment actually received. Statistical significance was set at $p \leq 0.05$ with 95% CIs for the primary outcome and at $p \leq 0.01$ with 99% CIs for secondary outcomes. All reported p-values are 2-sided. The main analysis was performed in SAS® software for Windows, version 9.4, SAS Institute Inc., Cary, USA. IBM SPSS for Windows version 22, Armonk, New York, USA was used for sensitivity analyses.

Interim analyses of safety and effectiveness were reviewed annually by an independent Data Monitoring and Safety Committee. No alpha-spending adjustments were made.

RESULTS

Participants

8003 participants from 136 collaborating centers in the UK were randomized and followed up between April 24th 2008 and January 27th 2015 (Figure 1). Baseline demographic and clinical characteristics, including stroke severity and oxygen saturation at randomization, were well balanced in the three groups (Table 1). The mean age of participants was 72 (SD 13) years, 4398 (55%) were male, and 7332 (92%) could undertake activities of daily living independently before the stroke. The mean/median NIHSS was 7/5 (SD 6/IQR 3-9). 1601 (20%) had been given oxygen prior to randomization, in the ambulance or in hospital. Patients were enrolled at a median 20h:43min (IQR 11:59–25:32) after symptom onset. The mean oxygen saturation at randomization was 96.6% (SD 1.7%). All participants had a clinical diagnosis of stroke at the time of enrolment. The final diagnosis at 7 days was ischemic stroke in most cases (n=6555, 82%), 588 (7%) had a primary intracerebral hemorrhage, and 294 (4%) were strokes without CT diagnosis. 168 (2%) were given a final diagnosis of transient ischemic attack, and 292 (4%) were found to have other non-stroke diagnoses, with missing data in 106 (1%).

6991 (87%) of participants gave fully informed consent and 1012 (13%) had consent given by a relative, carer, or an independent legal representative (eTable 1). Of the participants who were unable to consent themselves and were included by a representative, 6 (0.1%) refused consent at the 1-week reassessment and 22 (2%) at the 90-day assessment, and were withdrawn.

Treatment adherence

Adherence was similar in the continuous and night-time oxygen groups, with 2158 (81%) and 2225 (83%), respectively, prescribed oxygen for the full course of treatment (eTable 2). 433 (16%) participants in the continuous and 361 (14%) in the night-time group discontinued oxygen prematurely. The most common reason for early discontinuation of oxygen was discharge from hospital. In the control group, trial oxygen was recorded as being given in 33 (1.2%), with no recording of whether oxygen was given in 406 (15%).

Effect on oxygenation

Oxygen treatment resulted in a significant increase of 0.8% and 0.9% in the highest and lowest oxygen saturations, respectively, during the 72 h of the intervention period in the continuous oxygen group compared to controls, and of 0.5% and 0.4% for the highest and lowest oxygen saturations, respectively, in the nocturnal oxygen group compared to controls (p<0.001 for all comparisons, Table 2). Significantly more participants in the combined oxygen groups required oxygen for clinical reasons during the intervention period than in the control group: 9% (463) vs. 7% (176), p<0.001. Similarly, more participants in the continuous than nocturnal oxygen group required oxygen: 10% (254) vs. 8% (209), p=0.03.

Main outcome

The primary analysis demonstrated that oxygen supplementation did not significantly improve functional outcome at 90 days (Figure 2). The unadjusted OR for a better outcome (lower mRS) was 0.97 (95% CI 0.89–1.05, p=0.47) for combined oxygen versus control, and 1.03 (95% CI 0.93–1.13, p=0.61) for continuous oxygen versus nocturnal oxygen. Secondary analyses adjusted for age, sex, baseline NIHSS score, baseline oxygen saturation, and the SSV prognostic index yielded very similar results: OR=0.97 (95% CI 0.89–1.06, p=0.54) for the combined oxygen group versus control and OR=1.01 (95% CI 0.92–1.12, p=0.81) for continuous oxygen versus oxygen at night only. With similar numbers of missing responses in the continuous oxygen (n=101), nocturnal oxygen (n=106), and control groups (n=119), findings were much the same in sensitivity analyses using multiple imputation or analyzing adherers only (eTable 3).

Subgroup analysis (figure 3) found no indication that treatment effectiveness differed in any of the predefined subgroups, even those where most benefit might be expected – such as patients with more severe strokes or those for whom oxygen supplementation was started early after onset of stroke.

Secondary outcomes

Analyses of secondary outcomes also showed no benefit from oxygen (Table 2). Neurological impairment at one week improved from baseline to the same degree in all three groups, with median NIHSS scores of 2 (IQR 1–6) by one week. Oxygen treatment did not increase the number of participants who were alive and independent, or back in their home, the ability to perform basic (BI) or extended (NEADL) activities of daily living, or quality of life (EQ5D-3L) at 90 days. The results remained unchanged after adjustment for baseline prognostic factors (eTable 4). Mortality (figure 4) was similar in the oxygen (both groups combined) and control groups (hazard ratio [HR] =0.97 [99% CI 0.78–1.21], p=0.75), and for continuous oxygen versus oxygen at night only (HR=1.15 [99% CI 0.90–1.48], p=0.15).

Exploratory analyses

There was no evidence of increased stress levels (higher heart rates, higher blood pressure and need for sedation) in oxygen-treated participants than in controls, or that oxygen treatment was associated with more infections, with little differences in the highest temperature or the need for antibiotics (Table 2).

Safety outcomes

The number of serious adverse events by 90 days was similar in the combined oxygen and control groups, but lower in the nocturnal oxygen group when compared to continuous oxygen (Table 2 and eTable 5). No oxygen-related adverse events (respiratory depression, drying of mucous membranes) were reported.

DISCUSSION

The key finding of this trial is that routine prophylactic low-dose oxygen supplementation did not improve outcome in patients with acute stroke who were not hypoxic at baseline, whether given continuously for 72 hours or at night only. This applied to the primary 90-day functional outcome and to all other tested outcomes, including early neurological recovery, mortality, disability, independence in basic and extended activities of daily living, and quality of life. The results remained unchanged in analyses adjusted for baseline prognostic factors, and in sensitivity analyses using multiple imputation or analyzing adherers only. Subgroup analyses did not identify any characteristics that would make a patient more likely to benefit from oxygen treatment. This includes enrolment between 3-6 hours after onset, patients with a lower baseline oxygen saturation, severe strokes, a reduced level of consciousness, and a history of heart failure or lung disease; i.e. those characteristics for which benefit from oxygen was most anticipated. Because of the large overall size of this trial, these patient subgroups were each sufficiently large for the lack of observed benefit to be likely real and not a false negative.

In contrast to the much smaller SOS Pilot study,[15] this trial showed no evidence of better early neurological recovery with oxygen. Subgroup analysis of an earlier study of low-dose oxygen supplementation in acute stroke[14] suggested that oxygen might adversely affect outcome in patients with mild strokes, possibly through formation of toxic free radicals. A more recent study of short-burst high-flow oxygen (45L/min) was terminated early after enrolment of 85 patients because of excess mortality in the actively treated group.[13] Hyperoxia was independently associated with mortality in a large retrospective cohort study of ventilated patients with stroke.[28] While suggestive of potential harm, these findings could be due to confounding factors. This trial showed no difference in mortality, functional outcomes and adverse events and therefore provides reassuring evidence that low-dose oxygen supplementation is safe in patients with acute stroke.

As a large pragmatic trial, this study included patients with a clinical diagnosis of acute stroke, without radiological confirmation. The sample therefore included ischemic and hemorrhagic strokes, and participants who were later found to have mimics or transient ischemic attacks.

This trial was a large pragmatic study aimed at unselected patients with stroke. Over half of all acute stroke services in the UK participated and wide inclusion criteria allowed enrolment of a representative sample of ischemic and hemorrhagic patients with stroke across the whole range of severity. Stroke severity was similar to that of the UK stroke population as a whole, with a median NIHSS of 5 in this trial and 4 in the UK Sentinel Stroke National Audit Programme, which includes every stroke patient admitted to UK hospitals.[31] The median NIHSS of 127,950 patients with acute ischemic stroke in the US Get with the Guidelines Register[32] was 5, as in this trial. A median NIHSS of 5 at baseline was also recorded in a large Dutch study of antibiotic prophylaxis after stroke, with similarly wide inclusion criteria.[33]

This study has several limitations. Minor benefits from oxygen treatment might have been masked by poor compliance. However, this seems unlikely given the high statistical power to detect even small improvements. Moreover, sensitivity analyses did not show better outcomes in the adherers-only group (eTable 3). Furthermore, this trial found significant increases in the oxygen saturations in the treated groups compared to control. Patients with acute stroke are often restless and confused. Ensuring full adherence would ideally require 1:1 nursing. However, this is not possible outside an intensive care setting. The main outcome was assessed by postal questionnaire, supported by telephone interviews in non-responders. This method has been used successfully in large pragmatic trials,[29,30] but has been replaced by remote multiple-rater video-recorded interviews or in-person interview and examination by an allocation-blinded rater using formal structured assessments in several more recent studies. Low-dose oxygen supplementation may not be sufficient to prevent severe desaturations; both the SOS Pilot[15] and this trial found no significant difference in severe desaturations between the treatment and control groups. A small (n=46) non-randomized study comparing high-flow oxygen treatment via mask with low-flow supplementation via nasal cannulae showed a trend towards lower mortality with high flow. However, evidence from randomized trials of high-flow oxygen treatment in acute stroke[11,12,13] does not show that higher doses of oxygen are associated with better outcomes. Early administration of high-dose oxygen might help maintain the viability of the ischemic penumbra and allow a broader time window for neuroprotection or thrombolysis. This question was not addressed in this trial of prophylactic oxygen, but will be tested in the PROOF trial (http://www.safestroke.eu/proof-trial/).

The median time from stroke onset to randomization in this trial was 20h 43min. However, 101 participants were enrolled early (within 3 hours of symptom onset). Subgroup analysis (figure 3) showed a similar lack of effect for oxygen in the small subset of patients enrolled early as in those enrolled later, but was underpowered. Larger trials in the early time window would be needed to definitely exclude a benefit.

Conclusions

Among non-hypoxic patients with acute stroke the prophylactic use of low-dose oxygen supplementation did not reduce death or disability at 3 months. These findings do not support low-dose oxygen in this setting.

CONTRIBUTORS

CR and RG designed the trial. TN, CR, JS, NI, and RG ran the trial and CR recruited patients. Analyses were planned by NI, RG and JS and undertaken by JB and JS; PF reviewed the literature. CR, TN, JS and RG drafted the report and revised it with advice from all writing committee members.

DECLARATION OF INTERESTS

C. Roffe received lecture and travel fees from Air Liquide and is an independent member of the data safety and monitoring committee of the PROOF trial. There are no other competing interests.

ROLE OF THE FUNDING SOURCE

The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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TABLES

Table 1 Baseline characteristics

	Continuous oxygen n=2668	Nocturnal oxygen n=2667	Control n=2668
Demographic characteristics			
Age; (years); mean (SD)[a]	72 (13)	72 (13)	72 (13)
Male sex; *n* (%)	1466 (55)	1466 (55)	1466 (55)
Prognostic factors			
Living alone before the stroke; *n* (%)[a]	861 (32)	857 (32)	907 (34)
Independent in basic ADLs before the stroke; *n* (%)[a]	2451 (92)	2431 (91)	2450 (92)
Normal verbal response; *n* (%)[a]	2190 (82)	2207 (83)	2196 (82)
Able to lift both arms; *n* (%)[a]	1998 (75)	2022 (76)	1996 (75)
Able to walk; *n* (%)[a]	660 (25)	704 (26)	677 (25)
Probability of 30-day survival; median (IQR) [20]	0.92 (0.86-0.95)	0.92 (0.86-0.95)	0.92 (0.86-0.95)
Alive and independent at 6 m; *probability* median (IQR) [a] [20]	0.44 (0.12-0.71)	0.42 (0.12-0.71)	0.42 (0.12-0.71)
Blood glucose; mg/dl mean (SD)	127 (46)	126 (43)	128 (45)
Concomitant medical problems			
Ischemic heart disease; *n* (%)	573 (21)	515 (19)	514 (19)
Heart failure; *n* (%)	224 (8)	217 (8)	216 (8)
Atrial fibrillation; *n* (%)	638 (24)	673 (25)	684 (26)
Chronic obstructive pulmonary disease/asthma; *n* (%)	253 (9)	242 (9)	245 (9)
Other chronic lung problem; *n* (%)	29 (1)	24 (1)	19 (1)
Details of the qualifying event			
Time since symptom onset; hh:mm median (IQR) [a]	20:44 (11:53–25:33)	20:32 (12:05–25:31)	20:45 (11:57–25:31)
Diagnosis:			
Transient ischemic attack; *n* (%)[b]	52 (1.9)	50 (1.9)	66 (2.5)
Ischemic stroke; *n* (%)[b]	2187 (82.0)	2165 (81.1)	2203 (82.6)
Intracerebral hemorrhage; *n* (%)[b]	185 (6.9)	207 (7.8)	196 (7.3)
Stroke without imaging diagnosis; *n* (%)[b]	104 (3.9)	106 (4.0)	84 (3.1)
Not a stroke; *n* (%)[b]	101 (3.8)	98 (3.7)	93 (3.5)
Missing; *n* (%)[b]	39 (1.5)	41 (1.5)	26 (1.0)
Glasgow Coma Scale score (3–15); median (IQR) [range]	15 (15–15) [4-15]	15 (15–15) [5-15]	15 (15–15) [3-15]
Thrombolysed; *n* (%)[b]	447 (17)	410 (15)	447 (17)
NIHSS score (0–42); median (IQR)	5 (3–9)	5 (3–9)	5 (3–9)
Oxygenation			
Oxygen given prior to randomization; *n* (%)[a]	531 (20)	531 (20)	539 (20)
Oxygen saturation on room air; % mean (SD) [a]	96.6 (1.7)	96.6 (1.6)	96.7 (1.7)

Data in this table were collected before randomization with the exception of items marked with [b] which were recorded on day 7. Minimization variables are indicated by [a]. Activities of daily living (ADLs). The probability of being alive and independent was calculated using the 'six simple variables (SSV) prognostic index for independent survival at 6 months (m).[20] 'Normal verbal response' was taken from the verbal sub-item of the Glasgow Coma Scale. See online supplement eText 1 for definitions for diagnosis. The Glasgow Coma Scale score ranges from 3 (deep coma) to 15 (alert and oriented). The National Institutes for Heath Stroke Scale ranges from 0 (no deficit) to

42 (most severe deficit). Blood glucose was converted from mm/L to mg/dl by multiplying by a factor of 18.

Table 2 Secondary, exploratory and safety outcomes

	N=8003 (n)	Continuous oxygen n=2668	Nocturnal oxygen n=2667	Control n=2668	Comparison 1: Combined oxygen vs. control OR, MD, MdD or RR (99%CI); p-value	Comparison 2: Continuous vs. nocturnal OR, MD, MdD or RR (99%CI); p-value
Secondary outcomes at 72 hours						
Highest oxygen saturation (%)[a]	7860	99.1 (99.1-99.2)	98.8 (98.7-98.9)	98.3 (98.2-98.3)	MD 0.69 (0.61-0.77); p<0.0001[d]	MD 0.32 (0.22-0.41); p<0.0001[d]
Lowest oxygen saturation (%)[a]	7860	95.0 (94.9-95.1)	94.5 (94.4-94.6)	94.1 (94.0-94.2)	MD 0.62 (0.48-0.76); p<0.0001[d]	MD 0.48 (0.32-0.63); p<0.0001[d]
Oxygen saturation <90%[b]	7860	39 (1.5%)	30 (1.1%)	74 (2.8%)	OR 0.46 (0.30-0.71); p<0.0001[e]	OR 1.30 (0.69-2.44); p=0.28[e]
Oxygen saturation <95%[b]	7860	861 (32.9%)	1119 (42.9%)	1354 (51.5%)	OR 0.57 (0.51-0.65); p<0.0001[e]	OR 0.65 (0.56-0.76); p=<0.0001[e]
Need for additional oxygen[b]	7809	254 (9.8%)	209 (8.1%)	176 (6.7%)	OR 1.36 (1.07-1.73); p=0.0008[e]	OR 1.23 (0.96-1.59); p=0.03[e]
Secondary outcomes at 7 days						
National Institutes of Health Stroke Scale[c]	7778	2 (2–3)	2 (2–3)	2 (2–3)	MdD 0 (0–0); p=0.56[f]	MdD 0 (0–0); p=0.95[f]
Neurological improvement[b]	7778	1016 (39.2%)	1029 (39.7%)	1037 (39.9%)	OR 0.98 (0.86-1.11); p=0.68[e]	OR 0.98 (0.85-1.13); p=0.71[e]
Death by 7 days[b]	7959	50 (1.9%)	35 (1.3%)	45 (1.7%)	OR 0.95 (0.59-1.53); p=0.78[e]	OR 1.43 (0.81-2.54); p=0.11[e]
Secondary outcomes at 90 days						
Death by 90 days (mRS=6) [b]	7677	257 (10.0%)	236 (9.2%)	246 (9.7%)	OR 1.00 (0.81-1.23); p=0.96[e]	OR 1.10 (0.86-1.40); p=0.3[e]
Alive and independent (mRS≤2)[b]	7677	1325 (51.6%)	1316 (51.4%)	1337 (52.5%)	OR 0.96 (0.85-1.09); p=0.43[e]	OR 1.01 (0.87-1.17); p=0.87[e]
Living at home[b]	6859	1961 (85.8%)	1947 (84.8%)	1947 (85.4%)	OR 0.99 (0.82-1.20); p=0.91[e]	OR 1.08 (0.87-1.34); p=0.35[e]
Barthel ADL index [0 (worst)-100 (best)][a]	6549	70.2 (68.2-72.2)	71.1 (69.1-73.1)	70.9 (68.9-72.8)	MD -0.18 (-2.60-2.24); p=0.85[d]	MD -0.86 (-3.65-1.93); p=0.43[d]
Nottingham Extended ADL [0 (worst)–21 (best)][a]	7528	9.66 (9.29-10.02)	9.54 (9.17-9.90)	9.77 (9.40-10.14)	MD -0.17 (-0.62-0.28); p=0.32[d]	MD 0.12 (-0.40-0.64); p=0.55[d]

Table 2 continued	N=8003 (n)	Continuous oxygen n=2668	Nocturnal oxygen n=2667	Control n=2668	Comparison 1: Combined oxygen vs. control OR, MD, MdD or RR (99%CI); p-value	Comparison 2: Continuous vs. nocturnal OR, MD, MdD or RR (99%CI); p-value
Quality of life (EQ5D-3L) [-0.59 (worst)-1 (best)][a]	7248	0.50 (0.48-0.51)	0.50 (0.48-0.51)	0.49 (0.48-0.51)	MD 0.004 (-0.02-0.03) p=0.71[d]	MD 0.003 (-0.03-0.03) p=0.78[d]
Quality of life (VAS) [0 (worst)-100 (best)][a]	6675	55.4 (53.8-67.1)	55.7 (54.1-57.3)	55.5 (53.8-57.1)	MD 0.10 (-1.93-2.12); p=0.90[d]	MD -0.24 (-2.57-2.09) p=0.79[d]
Exploratory outcomes						
Highest heart rate within 72 hours (beats per minute)[a]	7859	87.2 (86.3-88.0)	88.0 (87.2-88.8)	87.7 (86.9-88.4)	MD -0.07 (-1.06-0.92)	MD -0.83 (-2.01-0.35)
Highest systolic BP within 72 hours (mm Hg)[a]	7864	162.4 (161.2-163.7)	162.8 (161.5-164.0)	164.6 (163.3-165.8)	MD -1.96 (-3.48-(-0.44))	MD -0.35 (-2.11-1.41)
Highest diastolic BP within 72 hours (mm Hg)[a]	7861	89.5 (88.7-90.2)	90.2 (89.4-90.0)	90.9 (90.1-91.7)	MD -1.10 (-2.06- (-0.15))	MD -0.72 (-1.82-0.37)
Highest temperature within 7days (Celsius)[a]	7877	37.1 (37.1-37.2)	37.2 (37.1-37.2)	37.1 (37.1-37.2)	MD 0.01 (-0.03-0.04)	MD -0.01 (-0.05-0.03)
Antibiotics given within 7 days [b]	7916	400 (15.2%)	393 (14.9%)	403 (15.2%)	OR 0.99 (0.83-1.17)	OR 1.02 (0.84-1.24)
Sedatives given within 7 days [b]	7916	140 (5.3%)	161 (6.1%)	154 (5.8%)	OR 0.98 (0.76-1.28)	OR 0.86 (0.63-1.17)
Sleep as good as before the stroke[b]	6584	1407 (64%)	1436 (65%)	1419 (65%)	OR 0.98 (0.85-1.13)	OR 0.96 (0.82-1.13)
No significant speech problems[b]	6716	1957 (88%)	1957 (87%)	1939 (87%)	OR 1.09 (0.89-1.32)	OR 1.06 (0.84-1.34)
Memory as good as before the stroke[b]	6646	981 (44%)	1000 (45%)	971 (44%)	OR 1.02 (0.89-1.16)	OR 0.97 (0.83-1.13)
Safety						
Serious adverse events (SAEs)[a]	8003	0.16 (0.14-0.18)	0.13 (0.11-0.16)	0.16 (0.13-0.18)	RR 0.94 (0.78-1.13); p=0.37[g]	RR 1.19 (0.96-1.47); p=0.03[g]
Participants with least one SAE[b]	8003	348 (13.0%)	294 (11.0%)	322 (12.1%)	OR 1.00 (0.83-1.20); p=0.96[e]	OR 1.21 (0.97-1.51); p=0.02[e]

Data are given as means and 99% confidence intervals,[a] numbers and percentages,[b] or medians and 99% confidence intervals.[c] Mean differences (MD) are reported for means, median differences (MdD) for medians, odds ratios (OR) for frequencies, and rate ratios (RR) for count data. ORs < 1 indicate that the outcome is less likely with oxygen than with control (reference category) in comparison 1 and less likely with continuous oxygen than with nocturnal oxygen (reference category) in comparison 2. Significance testing was by unrelated t-test[d] chi-squared test,[e] Wilcoxon rank sum test,[f] or negative binomial regression.[g] The highest and lowest oxygen saturations were the highest/lowest record of oxygen saturation on the participant's observation chart during the 72 hours after randomization. Neurological improvement is a decrease of 4 or more or to zero on the National Institutes of Health Stroke Scale (NIHSS). Death by 90 days is a modified Rankin Scale (mRS) score of 6. Alive and independent is a modified Rankin Scale score of 2 or less. Activities of daily living (ADL), quality of life (EQ5D-3L) and visual analogue scale (VAS). As outlined in the statistical analysis plan,[17] significance tests were not conducted on the exploratory data and the outcomes suggested by patients and carers. HR: heart rate.

FIGURE LEGENDS

Figure 1 Trial profile

This figure shows participant enrollment, withdrawals, and follow up. Data on the number of patients screened are not available.

Figure 2 Main outcome: modified Rankin Scale at 90 days

From the ordinal regression analysis the unadjusted odds ratio (OR) for a better outcome (lower mRS) was 0.97 (95% CI 0.89–1.05, p=0.47) for combined oxygen versus control, and 1.03 (95% CI 0.93–1.13, p=0.61) for continuous oxygen versus nightly oxygen. Modified Rankin Scale (mRS): 0 = no symptoms, 1=few symptoms, but able to carry out all previous activities and duties, 2 = unable to carry out all previous activities, but able to look after own affairs without assistance, 3 = needs some help with looking after own affairs, but able to walk without assistance, 4 = unable to walk without assistance and unable to attend to own bodily needs without assistance, but I does not need constant care and attention, 5 = major symptoms (bedridden and incontinent, needs constant attention day and night), 6 = death.

Figure 3 Subgroup analyses: mRS at 90 days oxygen versus control

Subgroup analyses are depicted as a forest plot; p-values relate to the test for interaction. The x-axis depicts the 'common' odds ratio (OR) for a better outcome over all 7 levels of the modified Rankin Scale score (mRS). It is derived from ordinal logistic regression. ORs > 1 indicate that a good outcome (low mRS) is more likely with oxygen than with control (reference category). n is the total number of participants in that subgroup category. The size of the markers reflects the total sample size in the subgroup concerned, with larger markers equating to more precise estimates. The subgroup thresholds for oxygen concentration at randomization were revised from the prespecified thresholds as the analysis did not converge using the prespecified values. NIHSS: National Institutes of Health Stroke Scale; TIA: transient ischemic attack; SSV: 'six simple variables' risk score; COPD: chronic obstructive pulmonary disease; CCF: congestive cardiac failure; GCS: Glasgow Coma Scale.

Figure 4 Mortality up to 90 days

This figure shows the probability of death in the control group (grey dashed line) and the combined oxygen group (black line) in the top panel. The bottom panel shows the probability of death in the nocturnal oxygen group (dashed grey line) and the probability of death in the continuous oxygen group (black line). The cut off for mortality for this figure was 90 days. This is different from the 90-day mortality reported in table 2 and Figure 2, where responses were accepted up to 6 months if 3-month outcomes were not returned. Median and [range] of duration of follow-up was 90 days [0-90] in each treatment group.