

## Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke

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DOI:

[10.1001/jama.2017.11463](https://doi.org/10.1001/jama.2017.11463)

### Document Version

Peer reviewed version

### Citation for published version (Harvard):

Roffe, C, Nevatte, T, Sim, J, Bishop, J, Ives, N, Ferdinand, P, Gray, R & Stroke Oxygen Study Investigators and the Stroke Oxygen Study Collaborative Group 2017, 'Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke: the stroke oxygen study randomized clinical trial', *JAMA The Journal of the American Medical Association*, vol. 318, no. 12, pp. 1125-1135.  
<https://doi.org/10.1001/jama.2017.11463>

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### Publisher Rights Statement:

Checked for eligibility: 26/01/2018  
<https://jamanetwork.com/journals/jama/fullarticle/2654819>  
doi:10.1001/jama.2017.11463

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1 **TITLE PAGE**

2

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

5

6 **Revision 2 10<sup>th</sup> August 2017, corrected**

7

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30 Word count: 3153

31 **KEY POINTS**

32

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

35

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

41

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

44

45 **ABSTRACT**

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

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

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

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

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

68 **Results:** 8003 patients (4398 (55%) males, mean age 72 (SD13) years; median NIHSS 5; mean  
69 baseline oxygen saturation 96.6%) were enrolled. The primary outcome was available in 7677  
70 (96%) participants. The unadjusted odds ratio for a better outcome (calculated via ordinal logistic  
71 regression) was 0.97 (95% CI 0.89–1.05), p=0.47 for oxygen versus control, and 1.03 (95% CI  
72 0.93–1.13), p=0.61 for continuous versus nocturnal oxygen. No subgroup could be identified that  
73 benefited from oxygen. There were 348 (13.0%), 294 (11.0%), and 322 (12.1%) participants with at  
74 least one serious adverse event in the continuous, nocturnal, and control groups respectively. No  
75 significant harms were identified.

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

79 **Trial Registration:** [ISRCTN52416964](https://www.clinicaltrials.gov/ct2/show/study?term=ISRCTN52416964)

80 **Funder:** Research for Patient Benefit Programme and Health Technology Assessment Programme,  
81 National Institute for Health Research, UK

82

83 **INTRODUCTION**

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

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

102 The primary aim of the Stroke Oxygen Study (SO<sub>2</sub>S) was to determine whether low-dose oxygen  
103 therapy during the first 3 days after an acute stroke improves outcome compared to usual care  
104 (oxygen only when needed). As oxygen may restrict mobility and interfere with daytime activities,  
105 the secondary hypothesis was that oxygen given at night only, when hypoxia is most likely, is more  
106 effective than continuous oxygen supplementation.

107

## 108 **METHODS**

### 109 **Study design**

110 This was a multi-center randomized clinical trial of oxygen supplementation with single-blind  
111 outcome assessment. The protocol (see online supplement),<sup>16</sup> statistical analysis plan (see online  
112 supplement),<sup>17</sup> and data collection forms<sup>18</sup> are published. Fully informed written or witnessed oral  
113 consent was given by the participants or, if they did not have capacity to consent, by a legal  
114 representative. The protocol was approved by the North Staffordshire Research Ethics Committee  
115 (06/Q2604/109).

### 116 **Participants**

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

### 120 **Randomization and interventions**

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

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

### 138 **Outcomes and blinding**

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

153 **Study size**

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

162 **Statistical analysis**

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

169 The mRS was analysed by ordinal logistic regression, which yields a ‘common’ odds ratio (OR) for  
170 a move from one level to the next better (lower) level with an odds ratio more than 1.00 indicating  
171 an improvement. For this and other outcome variables, a primary unadjusted analysis and a  
172 secondary covariate-adjusted analysis were performed. Adjusted analyses incorporated the  
173 following covariates: age, sex, baseline NIHSS score, baseline oxygen saturation, and the SSV  
174 prognostic index for 6-month independence (or for analysis of mortality, the SSV prognostic index  
175 for 30-day survival). Sensitivity analysis for the mRS used multiple imputation of missing values  
176 (using a chained equations method, with 20 imputed datasets). Additional imputations were  
177 performed to allow for the possibility that data were missing not at random and were either i) better

178 or ii) worse than expected; missing values were thereby replaced by either very good (i.e. lowest) or  
179 very poor (i.e. highest) scores on the mRS, as appropriate (see eTable 3 in supplementary  
180 appendix). Subgroups, for the mRS only, were analysed by an interaction term, and were predefined  
181 in the statistical analysis plan<sup>17</sup> (see figure 2 for details of subgroups).  
182 For continuous outcomes, means and standard deviations (SD) or medians and interquartile ranges  
183 (IQR) are reported, as appropriate. Unadjusted analyses used unrelated t-tests, with the mean  
184 difference between treatments and corresponding confidence interval (CI) reported. The adjusted  
185 analysis used analysis of covariance, with the covariates specified earlier included in the analysis.  
186 For dichotomous outcomes, percentages were compared across the treatment comparisons using a  
187 chi-squared test (unadjusted analyses). Adjusted analyses of dichotomous outcomes used binary  
188 logistic regression, with the covariates listed earlier; ORs and confidence intervals are reported.  
189 All analyses were by intention to treat, i.e. according to the treatment group to which participants  
190 were allocated, irrespective of treatment actually received. Statistical significance was set at  $p \leq 0.05$   
191 with 95% CIs for the primary outcome and at  $p \leq 0.01$  with 99% CIs for secondary outcomes. All  
192 reported p-values are 2-sided. The main analysis was performed in SAS® software for Windows,  
193 version 9.4, SAS Institute Inc., Cary, USA. IBM SPSS for Windows version 22, Armonk, New  
194 York, USA was used for sensitivity analyses.  
195 Interim analyses of safety and effectiveness were reviewed annually by an independent Data  
196 Monitoring and Safety Committee. No alpha-spending adjustments were made.

197

## 198 **RESULTS**

### 199 **Participants**

200 8003 participants from 136 collaborating centers in the UK were randomized and followed up  
201 between April 24<sup>th</sup> 2008 and January 27<sup>th</sup> 2015 (Figure 1). Baseline demographic and clinical

202 characteristics, including stroke severity and oxygen saturation at randomization, were well  
203 balanced in the three groups (Table 1). The mean age of participants was 72 (SD 13) years, 4398  
204 (55%) were male, and 7332 (92%) could undertake activities of daily living independently before  
205 the stroke. The mean/median NIHSS was 7/5 (SD 6/IQR 3-9). 1601 (20%) had been given oxygen  
206 prior to randomization, in the ambulance or in hospital. Patients were enrolled at a median  
207 20h:43min (IQR 11:59–25:32) after symptom onset. The mean oxygen saturation at randomization  
208 was 96.6% (SD 1.7%). All participants had a clinical diagnosis of stroke at the time of enrolment.  
209 The final diagnosis at 7 days was ischemic stroke in most cases (n=6555, 82%), 588 (7%) had a  
210 primary intracerebral hemorrhage, and 294 (4%) were strokes without CT diagnosis. 168 (2%) were  
211 given a final diagnosis of transient ischemic attack, and 292 (4%) were found to have other non-  
212 stroke diagnoses, with missing data in 106 (1%).

213 6991 (87%) of participants gave fully informed consent and 1012 (13%) had consent given by a  
214 relative, carer, or an independent legal representative (eTable 1). Of the participants who were  
215 unable to consent themselves and were included by a representative, 6 (0.1%) refused consent at the  
216 1-week reassessment and 22 (2%) at the 90-day assessment, and were withdrawn.

### 217 **Treatment adherence**

218 Adherence was similar in the continuous and night-time oxygen groups, with 2158 (81%) and 2225  
219 (83%), respectively, prescribed oxygen for the full course of treatment (eTable 2). 433 (16%)  
220 participants in the continuous and 361 (14%) in the night-time group discontinued oxygen  
221 prematurely. The most common reason for early discontinuation of oxygen was discharge from  
222 hospital. In the control group, trial oxygen was recorded as being given in 33 (1.2%), with no  
223 recording of whether oxygen was given in 406 (15%).

224 **Effect on oxygenation**

225 Oxygen treatment resulted in a significant increase of 0.8% and 0.9% in the highest and lowest  
226 oxygen saturations, respectively, during the 72 h of the intervention period in the continuous  
227 oxygen group compared to controls, and of 0.5% and 0.4% for the highest and lowest oxygen  
228 saturations, respectively, in the nocturnal oxygen group compared to controls ( $p < 0.001$  for all  
229 comparisons, Table 2). Significantly more participants in the combined oxygen groups required  
230 oxygen for clinical reasons during the intervention period than in the control group: 9% (463) vs.  
231 7% (176),  $p < 0.001$ . Similarly, more participants in the continuous than nocturnal oxygen group  
232 required oxygen: 10% (254) vs. 8% (209),  $p = 0.03$ .

233 **Main outcome**

234 The primary analysis demonstrated that oxygen supplementation did not significantly improve  
235 functional outcome at 90 days (Figure 2). The unadjusted OR for a better outcome (lower mRS)  
236 was 0.97 (95% CI 0.89–1.05,  $p = 0.47$ ) for combined oxygen versus control, and 1.03 (95% CI 0.93–  
237 1.13,  $p = 0.61$ ) for continuous oxygen versus nocturnal oxygen. Secondary analyses adjusted for age,  
238 sex, baseline NIHSS score, baseline oxygen saturation, and the SSV prognostic index yielded very  
239 similar results: OR=0.97 (95% CI 0.89–1.06,  $p = 0.54$ ) for the combined oxygen group versus  
240 control and OR=1.01 (95% CI 0.92–1.12,  $p = 0.81$ ) for continuous oxygen versus oxygen at night  
241 only. With similar numbers of missing responses in the continuous oxygen ( $n = 101$ ), nocturnal  
242 oxygen ( $n = 106$ ), and control groups ( $n = 119$ ), findings were much the same in sensitivity analyses  
243 using multiple imputation or analyzing adherers only (eTable 3).

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

248 **Secondary outcomes**

249 Analyses of secondary outcomes also showed no benefit from oxygen (Table 2). Neurological  
250 impairment at one week improved from baseline to the same degree in all three groups, with median  
251 NIHSS scores of 2 (IQR 1–6) by one week. Oxygen treatment did not increase the number of  
252 participants who were alive and independent, or back in their home, the ability to perform basic (BI)  
253 or extended (NEADL) activities of daily living, or quality of life (EQ5D-3L) at 90 days. The results  
254 remained unchanged after adjustment for baseline prognostic factors (eTable 4). Mortality (figure 4)  
255 was similar in the oxygen (both groups combined) and control groups (hazard ratio [HR] =0.97  
256 [99% CI 0.78–1.21], p=0.75), and for continuous oxygen versus oxygen at night only (HR=1.15  
257 [99% CI 0.90–1.48], p=0.15).

258 **Exploratory analyses**

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

263 **Safety outcomes**

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

268

269 **DISCUSSION**

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

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

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

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

305 This study has several limitations. Minor benefits from oxygen treatment might have been masked  
306 by poor compliance. However, this seems unlikely given the high statistical power to detect even  
307 small improvements. Moreover, sensitivity analyses did not show better outcomes in the adherers-  
308 only group (eTable 3). Furthermore, this trial found significant increases in the oxygen saturations  
309 in the treated groups compared to control. Patients with acute stroke are often restless and confused.  
310 Ensuring full adherence would ideally require 1:1 nursing. However, this is not possible outside an  
311 intensive care setting. The main outcome was assessed by postal questionnaire, supported by  
312 telephone interviews in non-responders. This method has been used successfully in large pragmatic  
313 trials,<sup>29,30</sup> but has been replaced by remote multiple-rater video-recorded interviews or in-person  
314 interview and examination by an allocation-blinded rater using formal structured assessments in  
315 several more recent studies. Low-dose oxygen supplementation may not be sufficient to prevent  
316 severe desaturations; both the SOS Pilot<sup>15</sup> and this trial found no significant difference in severe

317 desaturations between the treatment and control groups. A small (n=46) non-randomized study  
318 comparing high-flow oxygen treatment via mask with low-flow supplementation via nasal cannulae  
319 showed a trend towards lower mortality with high flow. However, evidence from randomized trials  
320 of high-flow oxygen treatment in acute stroke<sup>11,12,13</sup> does not show that higher doses of oxygen are  
321 associated with better outcomes. Early administration of high-dose oxygen might help maintain the  
322 viability of the ischemic penumbra and allow a broader time window for neuroprotection or  
323 thrombolysis. This question was not addressed in this trial of prophylactic oxygen, but will be  
324 tested in the PROOF trial (<http://www.safestroke.eu/proof-trial/>).

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

### 330 **Conclusions**

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

334

### 335 **CONTRIBUTORS**

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

340

341 **DECLARATION OF INTERESTS**

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

344

345 **ROLE OF THE FUNDING SOURCE**

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

349

350 **ACKNOWLEDGEMENTS**

351 This project was funded by the National Institute for Health Research Health Technology  
352 Assessment (project number 09/104/21). The views and opinions expressed therein are those of the  
353 authors and do not necessarily reflect those of the Health Technology Assessment, NIHR, NHS or  
354 the Department of Health. SO<sub>2</sub>S was sponsored by North Staffordshire Combined Healthcare NHS  
355 Trust.

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581

## 582 TABLES

583

584 Table 1 Baseline characteristics

585

	Continuous oxygen n=2668	Nocturnal oxygen n=2667	Control n=2668
<b>Demographic characteristics</b>			
Age; (years); mean (SD) <sup>a</sup>	72 (13)	72 (13)	72 (13)
Male sex; n (%)	1466 (55)	1466 (55)	1466 (55)
<b>Prognostic factors</b>			
Living alone before the stroke; n (%) <sup>a</sup>	861 (32)	857 (32)	907 (34)
Independent in basic ADLs before the stroke; n (%) <sup>a</sup>	2451 (92)	2431 (91)	2450 (92)
Normal verbal response; n (%) <sup>a</sup>	2190 (82)	2207 (83)	2196 (82)
Able to lift both arms; n (%) <sup>a</sup>	1998 (75)	2022 (76)	1996 (75)
Able to walk; n (%) <sup>a</sup>	660 (25)	704 (26)	677 (25)
Probability of 30-day survival; median (IQR) <sup>20</sup>	0.92 (0.86-0.95)	0.92 (0.86-0.95)	0.92 (0.86-0.95)
Alive and independent at 6 m; <i>probability</i> median (IQR) <sup>a 20</sup>	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)
<b>Concomitant medical problems</b>			
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)
<b>Details of the qualifying event</b>			
Time since symptom onset; hh:mm median (IQR) <sup>a</sup>	20:44 (11:53–25:33)	20:32 (12:05–25:31)	20:45 (11:57–25:31)
Diagnosis:			
Transient ischemic attack; n (%) <sup>b</sup>	52 (1.9)	50 (1.9)	66 (2.5)
Ischemic stroke; n (%) <sup>b</sup>	2187 (82.0)	2165 (81.1)	2203 (82.6)
Intracerebral hemorrhage; n (%) <sup>b</sup>	185 (6.9)	207 (7.8)	196 (7.3)
Stroke without imaging diagnosis; n (%) <sup>b</sup>	104 (3.9)	106 (4.0)	84 (3.1)
Not a stroke; n (%) <sup>b</sup>	101 (3.8)	98 (3.7)	93 (3.5)
Missing; n (%) <sup>b</sup>	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 (%) <sup>b</sup>	447 (17)	410 (15)	447 (17)
NIHSS score (0–42); median (IQR)	5 (3–9)	5 (3–9)	5 (3–9)
<b>Oxygenation</b>			
Oxygen given prior to randomization; n (%) <sup>a</sup>	531 (20)	531 (20)	539 (20)
Oxygen saturation on room air; % mean (SD) <sup>a</sup>	96.6 (1.7)	96.6 (1.6)	96.7 (1.7)

586

587 Data in this table were collected before randomization with the exception of items marked with <sup>b</sup>  
588 which were recorded on day 7. Minimization variables are indicated by <sup>a</sup>. Activities of daily living  
589 (ADLs). The probability of being alive and independent was calculated using the ‘six simple  
590 variables (SSV) prognostic index for independent survival at 6 months (m).<sup>20</sup> ‘Normal verbal  
591 response’ was taken from the verbal sub-item of the Glasgow Coma Scale. See online supplement  
592 eText 1 for definitions for diagnosis. The Glasgow Coma Scale score ranges from 3 (deep coma) to  
593 15 (alert and oriented). The National Institutes for Health Stroke Scale ranges from 0 (no deficit) to

594 42 (most severe deficit). Blood glucose was converted from mm/L to mg/dl by multiplying by a  
595 factor of 18.  
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**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 (%) <sup>a</sup>	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 <sup>d</sup>	MD 0.32 (0.22-0.41); p<0.0001 <sup>d</sup>
Lowest oxygen saturation (%) <sup>a</sup>	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 <sup>d</sup>	MD 0.48 (0.32-0.63); p<0.0001 <sup>d</sup>
Oxygen saturation <90% <sup>b</sup>	7860	39 (1.5%)	30 (1.1%)	74 (2.8%)	OR 0.46 (0.30-0.71); p<0.0001 <sup>e</sup>	OR 1.30 (0.69-2.44); p=0.28 <sup>e</sup>
Oxygen saturation <95% <sup>b</sup>	7860	861 (32.9%)	1119 (42.9%)	1354 (51.5%)	OR 0.57 (0.51-0.65); p<0.0001 <sup>e</sup>	OR 0.65 (0.56-0.76); p<0.0001 <sup>e</sup>
Need for additional oxygen <sup>b</sup>	7809	254 (9.8%)	209 (8.1%)	176 (6.7%)	OR 1.36 (1.07-1.73); p=0.0008 <sup>e</sup>	OR 1.23 (0.96-1.59); p=0.03 <sup>e</sup>
Secondary outcomes at 7 days						
National Institutes of Health Stroke Scale <sup>c</sup>	7778	2 (2-3)	2 (2-3)	2 (2-3)	MdD 0 (0-0); p=0.56 <sup>f</sup>	MdD 0 (0-0); p=0.95 <sup>f</sup>
Neurological improvement <sup>b</sup>	7778	1016 (39.2%)	1029 (39.7%)	1037 (39.9%)	OR 0.98 (0.86-1.11); p=0.68 <sup>e</sup>	OR 0.98 (0.85-1.13); p=0.71 <sup>e</sup>
Death by 7 days <sup>b</sup>	7959	50 (1.9%)	35 (1.3%)	45 (1.7%)	OR 0.95 (0.59-1.53); p=0.78 <sup>e</sup>	OR 1.43 (0.81-2.54); p=0.11 <sup>e</sup>
Secondary outcomes at 90 days						
Death by 90 days (mRS=6) <sup>b</sup>	7677	257 (10.0%)	236 (9.2%)	246 (9.7%)	OR 1.00 (0.81-1.23); p=0.96 <sup>e</sup>	OR 1.10 (0.86-1.40); p=0.3 <sup>e</sup>
Alive and independent (mRS≤2) <sup>b</sup>	7677	1325 (51.6%)	1316 (51.4%)	1337 (52.5%)	OR 0.96 (0.85-1.09); p=0.43 <sup>e</sup>	OR 1.01 (0.87-1.17); p=0.87 <sup>e</sup>
Living at home <sup>b</sup>	6859	1961 (85.8%)	1947 (84.8%)	1947 (85.4%)	OR 0.99 (0.82-1.20); p=0.91 <sup>e</sup>	OR 1.08 (0.87-1.34); p=0.35 <sup>e</sup>
Barthel ADL index [0 (worst)-100 (best)] <sup>a</sup>	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 <sup>d</sup>	MD -0.86 (-3.65-1.93); p=0.43 <sup>d</sup>
Nottingham Extended ADL [0 (worst)-21 (best)] <sup>a</sup>	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 <sup>d</sup>	MD 0.12 (-0.40-0.64); p=0.55 <sup>d</sup>

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)] <sup>a</sup>	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 <sup>d</sup>	MD 0.003 (-0.03-0.03) p=0.78 <sup>d</sup>
Quality of life (VAS) [0 (worst)-100 (best)] <sup>a</sup>	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 <sup>d</sup>	MD -0.24 (-2.57-2.09) p=0.79 <sup>d</sup>
Exploratory outcomes						
Highest heart rate within 72 hours (beats per minute) <sup>a</sup>	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) <sup>a</sup>	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) <sup>a</sup>	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 7 days (Celsius) <sup>a</sup>	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 <sup>b</sup>	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 <sup>b</sup>	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 <sup>b</sup>	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 <sup>b</sup>	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 <sup>b</sup>	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) <sup>a</sup>	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 <sup>g</sup>	RR 1.19 (0.96-1.47); p=0.03 <sup>g</sup>
Participants with least one SAE <sup>b</sup>	8003	348 (13.0%)	294 (11.0%)	322 (12.1%)	OR 1.00 (0.83-1.20); p=0.96 <sup>c</sup>	OR 1.21 (0.97-1.51); p=0.02 <sup>c</sup>

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Data are given as means and 99% confidence intervals,<sup>a</sup> numbers and percentages,<sup>b</sup> or medians and 99% confidence intervals.<sup>c</sup> 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<sup>d</sup> chi-squared test,<sup>e</sup> Wilcoxon rank sum test,<sup>f</sup> or negative binomial regression.<sup>g</sup> 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,<sup>17</sup> significance tests were not conducted on the exploratory data and the outcomes suggested by patients and carers. HR: heart rate.

## 613 **FIGURE LEGENDS**

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### 615 **Figure 1 Trial profile**

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

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### 619 **Figure 2 Main outcome: modified Rankin Scale at 90 days**

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621 From the ordinal regression analysis the unadjusted odds ratio (OR) for a better outcome  
622 (lower mRS) was 0.97 (95% CI 0.89–1.05,  $p=0.47$ ) for combined oxygen versus control, and  
623 1.03 (95% CI 0.93–1.13,  $p=0.61$ ) for continuous oxygen versus nightly oxygen. Modified  
624 Rankin Scale (mRS): 0 = no symptoms, 1=few symptoms, but able to carry out all previous  
625 activities and duties, 2 = unable to carry out all previous activities, but able to look after own  
626 affairs without assistance, 3 = needs some help with looking after own affairs, but able to  
627 walk without assistance, 4 = unable to walk without assistance and unable to attend to own  
628 bodily needs without assistance, but I does not need constant care and attention, 5 = major  
629 symptoms (bedridden and incontinent, needs constant attention day and night), 6 = death.

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

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

### 643 **Figure 4 Mortality up to 90 days**

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