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| Question |
| **Should use of supplementary oxygen vs. no use of supplementary oxygen be used for adult with suspected acute stroke?** |
| **Population:** | Adults with suspected acute stroke |
| **Intervention:** | Use of supplementary oxygen |
| **Comparison:** | No use of supplementary oxygen (room air) |
| **Main outcomes:** | * Survival at 1 week, 3 months, 6 months, or 1 year
* National Institute of Health Stroke Scale (NIHSS) difference between baseline and 1 week
* National Institute of Health Stroke Scale (NIHSS) at 1 week, 3 months
* % of Patients with NIHSS improvement >4 at 1 week
* Modified Rankin Score (mRS) <3 at 6 months (degree of disability/dependence, higher is better)
* mRS at 1 week, 3 months, 6 months
* Barthel index at 1 week, 3 months, 6 months, 7 months (degree of independence, higher is better)
* Scandinavian Stroke Scale (SSS) at 3 months, 7 months
* Lesion volume change on imaging at 4 hours, 24 hours, or discharge
* Requirement for non-invasive positive pressure ventilation, intubation and mechanical ventilation
* Respiratory complications, including ARDS, pulmonary edema, pneumonia, respiratory failure; treatment for hospital-acquired pneumonia, any documentation of pneumonia at discharge.
 |
| **Setting:** | In the prehospital or in-hospital setting |
| **Perspective:** | Perspective of individuals with acute stroke as well as first aid providers or first responders |
| **Background:** | Supplementary oxygen for patients with acute stroke has traditionally been regarded as beneficial. It is believed that raising the oxygen level in the circulation may help oxygen diffusion into the penumbra surrounding the stroke core, thereby rescuing the ischemic brain tissue and minimizing the area of ischemic-hypoxic neuronal injury. Most of all, this may potentially extend the therapeutic time window for further therapeutic interventions such as thrombolysis. There have been a number of studies exploring the effects of supplementary oxygen in acute stroke, however, the results are controversial. Concerns have arisen as to whether supplementary oxygen would increase the risk of oxidative injury to the reperfused brain tissue and worsen neurological outcome. Therefore, a systematic review and meta-analysis of the role of supplementary oxygen in acute stroke is considered a high priority question by FATF. Although use of oxygen is not considered standard first aid, oxygen can be used by first aid providers with specialized training (i.e., First Aid Oxygen courses). The routes of supplementary oxygen appropriate for first aid include oxygen by nasal cannula and oxygen mask.  |
| **Conflict of interests:** | None declared. |

# Assessment

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| ProblemIs the problem a priority? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes● Yes○ Varies○ Don't know | Stroke is a major cause of long-term disability and the second most common cause of death in the developed countries worldwide (Feigin 2014 245). The associated long-term disability exerts variable socio-economic impact on the patient, family, and society.  | Supplementary oxygen for patients with acute stroke has traditionally been regarded as beneficial. It is believed that raising the oxygen level in the circulation may help oxygen diffusion into the penumbra surrounding the stroke core, thereby rescuing the ischemic brain tissue and minimizing the area of ischemic-hypoxic neuronal injury. Most of all, this may potentially extend the therapeutic time window for further therapeutic interventions such as thrombolysis. There have been a number of studies exploring the effects of supplementary oxygen in acute stroke, however, the results are controversial. Concerns have arisen as to whether supplementary oxygen would increase the risk of oxidative injury to the reperfused brain tissue and worsen neurological outcome.  |
| Desirable EffectsHow substantial are the desirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ● Trivial○ Small○ Moderate○ Large○ Varies○ Don't know | For the critical neurological outcome of improvement of National Institute of Health Stroke Scale (NIHSS) of more than 4 at one week, a single randomized controlled trial (Roffe 2011 1297) showed benefit with the use of supplementary oxygen at 2-3 L/min via nasal cannula for 72h compared with room air (RR 2.19, 95% C.I. 1.37 to 3.51).For the critical neurological outcome of Scandinavian stroke scale (SSS) at 7 months, a single randomized controlled trial (Ronning 1999 408) showed benefit with use of supplementary oxygen at 3 L/min via nasal cannula for 24h compared with room air (absolute difference, -0.50 points lower, 95% CI -0.98 lower to -0.02 points lower).For the critical outcome of survival at one week, 3 months, 6 months and 1 year, the included studies showed no difference with use of oxygen compared with room air/no oxygen. For the critical neurological outcome of National Institute of Health Stroke Scale (NIHSS) at one week and 3 months, the included studies showed no difference with use of oxygen compared with room air/no oxygen. | In summary, all but two of the included studies show no difference in outcomes of survival, NIHSS and modified Rankin scale scores at various times post injury with the use of supplementary oxygen compared with no use of oxygen/room air. |
| Undesirable EffectsHow substantial are the undesirable anticipated effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Large○ Moderate○ Small● Trivial○ Varies○ Don't know |   | In summary, there were no differences in outcomes of complications or survival with use of supplementary oxygen compared with no use of oxygen/room air. Respiratory complications including pneumonia and ARDS were only reported in a single observational study.  |
| Certainty of evidenceWhat is the overall certainty of the evidence of effects? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low● Moderate○ High○ No included studies | There is only one retrospective study performed in the prehospital setting to inform the treatment recommendation. This is supported by eight RCTs from the in-hospital setting that were all downgraded for indirectness.Only two outcomes, NIHSS improvement of more than 4 at one week and Scandinavian stroke scale (SSS) at 7 months, showed a significant difference while all the other outcomes have no difference between oxygen and no oxygen groups.There were important limitations in indirectness, study design and Inconsistency. |  |
| ValuesIs there important uncertainty about or variability in how much people value the main outcomes? |
| Judgement | Research evidence | Additional considerations |
| ○ Important uncertainty or variability○ Possibly important uncertainty or variability● Probably no important uncertainty or variability○ No important uncertainty or variability | No research evidence identified. | The administration of oxygen in a first aid setting may delay other care considerations that a person may value such as calling the designated emergency number (e.g. 911) or appropriate positioning.From a psychological perspective, the use of oxygen in the first aid setting may offer the patient some feeling of comfort that something is done vs sitting and waiting for EMS, assuming there is no harm.  |
| Balance of effectsDoes the balance between desirable and undesirable effects favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison○ Probably favors the comparison● Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies○ Don't know | Only two outcomes, NIHSS improvement of more than 4 at one week and Scandinavian stroke scale (SSS) at 7 months, showed significant improvement. There was no difference between use of use of oxygen and no oxygen for all other critical outcomes. | Although there are essentially no beneficial or harmful outcomes (i.e., research equipoise) with the use of oxygen compared with room air/no use of oxygen, the Task Force consensus opinion is that the balance of effect leans towards not using oxygen due to important concerns about the low certainty of evidence (indirectness of the included RCTs), lack of direct evidence (one prehospital observational study), feasibility of use of oxygen in the first setting, resources and training required, and reduced health equity in some geographic regions. An additional concern is the potential for the assembly and application of oxygen to distract a first aid provider from other important interventions such as calling for help or positioning the person with a suspected acute stroke. |
| Resources requiredHow large are the resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Large costs●**Moderate costs**○ Negligible costs and savings○ Moderate savings○ Large savings○ Varies○ Don't know | No research identified. | To use supplementary oxygen for adults with suspected acute stroke in the first aid setting, there may be challenges with resources. Oxygen equipment is needed (i.e., tank, tubing, pressure regulator) and nasal cannula or face masks, and there needs to be a means of carrying the equipment as well as storing it. In some countries, first aid providers must take a special first aid oxygen use course and obtain certification for use. A license and prescription for oxygen is required in some countries or provinces. Additionally, while the cost for oxygen supply and delivery equipment varies by country, it may be considerable.  |
| Certainty of evidence of required resourcesWhat is the certainty of the evidence of resource requirements (costs)? |
| Judgement | Research evidence | Additional considerations |
| ○ Very low○ Low○ Moderate○ High● No included studies | No research identified. |  |
| Cost effectivenessDoes the cost-effectiveness of the intervention favor the intervention or the comparison? |
| Judgement | Research evidence | Additional considerations |
| ○ Favors the comparison● **Probably favors the comparison**○ Does not favor either the intervention or the comparison○ Probably favors the intervention○ Favors the intervention○ Varies○ No included studies | No research identified. | Because there is no benefit demonstrated in terms of the included outcomes with use of supplementary oxygen compared with no oxygen/room air, it is likely more cost-effective to use available room air. |
| EquityWhat would be the impact on health equity? |
| Judgement | Research evidence | Additional considerations |
| ○ Reduced●**Probably reduced**○ Probably no impact○ Probably increased○ Increased○ Varies○ Don't know | No research identified. | The additional requirement of purchasing oxygen equipment and supplies for use in possible stroke would potentially decrease health equity in many parts of the world. Required training and certification in use would also come at a cost.  |
| AcceptabilityIs the intervention acceptable to key stakeholders? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no● Probably yes○ Yes○ Varies○ Don't know | No research identified. | A person with symptoms of a possible stroke and their family members will likely accept the use of supplementary oxygen. Care providers would need to be willing to obtain additional training or certification as well as maintain oxygen delivery systems and supplies. |
| FeasibilityIs the intervention feasible to implement? |
| Judgement | Research evidence | Additional considerations |
| ○ No○ Probably no○ Probably yes○ Yes● Varies○ Don't know | No research identified | Feasibility is dependent upon the resources. It may be feasible to stock and use oxygen in facilities that are more likely to see stroke in their population, i.e., retirement or senior centers. On the other hand, as a first aid provider or first responder, it may not be feasible to carry an oxygen tank and delivery equipment, and the additional training /certification/licensing requirements are considerable and a significant potential barrier to implementation. |

# Summary of judgements

|  | **Judgement** |
| --- | --- |
| **Problem** | No | Probably no | Probably yes | **Yes** |  | Varies | Don't know |
| **Desirable Effects** | **Trivial** | Small | Moderate | Large |  | Varies | Don't know |
| **Undesirable Effects** | Large | Moderate | Small | **Trivial** |  | Varies | Don't know |
| **Certainty of evidence** | Very low | **Low** | Moderate | High |  |  | No included studies |
| **Values** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability |  |  |  |
| **Balance of effects** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **Resources required** | Large costs | **Moderate costs** | Negligible costs and savings | Moderate savings | Large savings | Varies | Don't know |
| **Certainty of evidence of required resources** | Very low | Low | Moderate | High |  |  | **No included studies** |
| **Cost effectiveness** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **Equity** | Reduced | **Probably reduced** | **Probably no impact** | Probably increased | Increased | Varies | Don't know |
| **Acceptability** | No | Probably no | **Probably yes** | Yes |  | Varies | Don't know |
| **Feasibility** | No | **Probably no** | Probably yes | Yes |  | **Varies** | Don't know |

# Type of recommendation

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| --- | --- | --- | --- | --- |
| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
| ○  | **●**  | ○  | ○  | ○  |

# Conclusions

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| Recommendation |
| For adults with suspected acute stroke, we suggest against the routine use of supplementary oxygen in the first aid setting in comparison with room air (weak recommendation, low to moderate certainty of evidence). |
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| Justification |
| In making this recommendation, the First Aid Task Force recognizes that the direct evidence comes from a single study in the prehospital setting but is supported indirectly by 8 RCTs from the in-hospital setting. The evidence overall shows research equipoise: no benefit or harm is demonstrated in nearly all included studies for the included outcomes with the use of supplementary oxygen for suspected stroke compared with no oxygen (use of room air). The balance of effects, however, changes when considering certainty of evidence, resource requirements, cost and potential impact on health equity, acceptability by all stakeholders and feasibility, particularly from an international perspective.The Task Force recognizes that the use of supplementary oxygen in the first aid setting or by first responders requires additional specialized training and certification or licensing in first aid oxygen use, additional resources with their associated costs, and may not be feasible to use. The stocking, storage or transportation of equipment and supplies may not be feasible or acceptable to first aid providers or first responders. Concern was expressed by First Aid Task Force members that the attempt to set up and deliver oxygen may also delay other critical immediate care goals, such as calling a designated emergency number or transporting to a hospital.  |

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| Subgroup considerations |
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| Implementation considerations |
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| Monitoring and evaluation |
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| Research priorities |
| • There are no randomized controlled studies of supplementary oxygen for adults with suspected acute stroke in the prehospital setting.• There are no studies about the indication for supplementary oxygen according to the severity of signs and symptoms of acute stroke.• There are no studies about an optimal dose of supplementary oxygen or the timing of delivery for adults with suspected acute stroke.• There are no studies about the best device to administer supplementary oxygen for adults with suspected acute stroke, for example, nasal canula or face mask.• Additional research is required into the ability of a prehospital/first aid provider to recognize suspected acute stroke.• Additional research is required to explore training and recertification requirements for first aid providers to use oxygen safely. |

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Evidence Profile tables

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| NIHSS at 3 months |  |
| 2Padma 2010Singh 2005 | Randomized trial | serious risk of bias a | no serious inconsistency | serious indirectness b | serious imprecision c | none | 28 | 26 | - | -0.62 points lower (-2.79, 1.56) | ⨁◯◯◯Very low |
| MRS <3 at 6 months |  |
| 2Ali 2014Mazdeh 2015 | Randomized trial | serious risk of bias a | no serious inconsistency | serious indirectness b | no serious imprecision | none | 174 | 166 | 1.06 (0.84, 1.34) | - | ⨁⨁◯◯Low |
| MRS at 1 week |  |
| 1Padma 2010 | Randomized trial | serious risk of bias a | no serious inconsistency | serious indirectness b | serious imprecision c | none | 20 | 20 |  |  | ⨁◯◯◯ Very low |
| MRS at 3 months |  |
| 2Roffe 2017Padma 2010Singh 2015 | Randomized trial | no serious risk of bias | no serious inconsistency | serious indirectness b | no serious imprecision | none | 2668 | 2668 | 0.97 (0.89, 1.05) | - | ⨁⨁⨁◯ Moderate |
| 20 | 20 |  |  |
| 9 | 7 | - | 0.90 points lower (-2.84, 1.04) |
| MRS at 6 months |  |
| 2Mazdeh 2015Ali 2014 | Randomized trial | serious risk of bias a | no serious inconsistency | serious indirectness b | no serious imprecision | none | 174 | 166 | - | 0.22 points lower (-0.01, 0.45) | ⨁⨁◯◯Low |
| Barthel index at 1 week |  |
| 1Padma 2010 | Randomized trial | serious risk of bias a | no serious inconsistency | serious indirectness b | serious imprecision c | none | 20 | 20 |  |  | ⨁◯◯◯ Very low |
| Barthel index at 3 months |  |
| 1Padma 2010Roffe 2017 | Randomized trial | no serious risk of bias | no serious inconsistency | serious indirectness b | no serious imprecision | none | 20 | 20 |  |  | ⨁⨁⨁◯ Moderate |
| 2668 | 2668 | - | 0.70 points lower (-1.49, 2.89) |
| Nottingham Extended ADL at 3 months |
| 1Roffe 2017 | Randomized trial | no serious risk of bias | no serious inconsistency | serious indirectness b | no serious imprecision | none | 2668 | 2668 | - | 0.11 points lower (-0.28 , 0.50) | ⨁⨁⨁◯ Moderate |
| EQ5D-3L for quality of life at 3 months |
| 1Roffe 2017 | Randomized trial | no serious risk of bias | no serious inconsistency | serious indirectness b | no serious imprecision | none | 2668 | 2668 | - | 0.01 points higher (-0.03 , 0.01) | ⨁⨁⨁◯ Moderate |
| VAS for quality of life at 3 months |
| 1Roffe 2017 | Randomized trial | no serious risk of bias | no serious inconsistency | serious indirectness b | no serious imprecision | none | 2668 | 2668 | - | 0.10 points lower (-1.67 , 1.87) | ⨁⨁⨁◯ Moderate |
| Barthel index at 6 months |  |
| 1Mazdeh 2015 | Randomized trial | serious risk of bias a | no serious inconsistency | serious indirectness b | serious imprecision c | none | 26 | 25 | - | 7.70 points higher (-11.01, 26.41) | ⨁◯◯◯ Very low |
| Barthel index at 7 months |  |
| 1Ronning 1999 | Randomized trial | serious risk of bias a | no serious inconsistency | serious indirectness b | no serious imprecision | none | 292 | 258 | - | 5 points lower (-6.24, -3.76) | ⨁⨁◯◯ Low |
| SSS at 3 months |  |
| 1Singh 2015 | Randomized trial | no serious risk of bias | no serious inconsistency | serious indirectness b | Some imprecision c | none | 9 | 7 | - | 5 points higher (-5.65, 15.65) | ⨁⨁◯◯ Low |
| SSS at 7 months |  |
| 1Ronning 1999 | Randomized trial | serious risk of bias a | no serious inconsistency | serious indirectness b | no serious imprecision | none | 292 | 258 | - | 0.50 points lower (-0.98, -0.02)  | ⨁⨁◯◯ Low |
| Lesion change at 4 hours |  |
| 1Wu 2012 | Randomized trial | no serious risk of bias | no serious inconsistency | serious indirectness b | serious imprecision c | none | 10 | 6 | - | 63% higher(-16%, 142%)  | ⨁⨁◯◯ Low |
| Lesion change at 24 hours |  |
| 1Wu 2012 | Randomized trial | no serious risk of bias | no serious inconsistency | serious indirectness b | serious imprecision c | none | 10 | 6 | - | 57% higher (-60%, 174%) | ⨁⨁◯◯ Low |
| Lesion change at discharge |  |
| 1Wu 2012 | Randomized trial | no serious risk of bias | no serious inconsistency | serious indirectness b | serious imprecision c | none | 10 | 6 | - | 31% higher (-58%, 120%) | ⨁⨁◯◯ Low |
| Requiring non-invasive positive pressure ventilation |  |
| 1Dylla 2019 | Observational cohort | serious risk of bias a | no serious inconsistency | no serious indirectness | no serious imprecision | none | 360 | 848 | 1.57 (0.56,4.38) | - | ⨁◯◯◯ Very low |
| Requiring intubation and mechanical ventilation |  |
| 1Dylla 2019 | Observational cohort | serious risk of bias a | no serious inconsistency | no serious indirectness | no serious imprecision | none | 360 | 848 | 2.80 (2.11,3.70) | - | ⨁◯◯◯ Very low |
| Pulmonary edema |  |
| 1Dylla 2019 | Observational cohort | serious risk of bias a | no serious inconsistency | no serious indirectness | no serious imprecision | none | 360 | 848 | 1.41 (0.52,3.86) | - | ⨁◯◯◯ Very low |
| Treatment for Hospital acquired pneumonia |  |
| 1Dylla 2019 | Observational cohort | serious risk of bias a | no serious inconsistency | No serious indirectness | no serious imprecision | none | 360 | 848 | 0.50 (0.26,0.98) | - | ⨁◯◯◯ Very low |
| Any documentation of pneumonia at discharge |  |
| 1Dylla 2019 | Observational cohort | serious risk of bias a | no serious inconsistency | No serious indirectness | no serious imprecision | none | 360 | 848 | 1.77 (0.97,3.21) | - | ⨁◯◯◯ Very low |
| Any respiratory complications (ARDS, pulmonary edema, pneumonia, respiratory failure) |  |
| 1Dylla 2019 | Observational cohort | serious risk of bias a | no serious inconsistency | No serious indirectness | no serious imprecision | none | 360 | 848 | 1.92 (1.54,2.39) | - | ⨁◯◯◯ Very low |
| Favorable mRS (0-2) at discharge |
| 1Dylla 2019 | Observational cohort | serious risk of bias a | no serious inconsistency | No serious indirectness | no serious imprecision | none | 360 | 848 | 1.06 (0.84,1.33) | - | ⨁◯◯◯ Very low |

a Some concerns for RoB

b Not direct measure of oxygen given in first aid setting

c small sample size