Title Page

Title: Effect of a strategy of supraglottic airway device versus tracheal intubation during out-of-hospital cardiac arrest on functional outcome: the AIRWAYS-2 randomized clinical trial.

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Key Points

Question: Does an initial strategy of a supraglottic airway device for advanced airway management during non-traumatic out-of-hospital cardiac arrest (OHCA) result in a better functional outcome compared with tracheal intubation?

Findings: In this cluster-randomized trial that included 1,523 paramedics and 9,296 patients with OHCA, favorable functional outcome (modified Rankin Scale 0-3) at hospital discharge or after 30 days (if still hospitalised) occurred in 6.4% in the supraglottic airway group versus 6.8% in the tracheal intubation group, a difference that was not statistically significant.

Meaning: In this study, a strategy of supraglottic airway device for advanced airway management did not provide a superior functional outcome.

Abstract

Importance: The optimal approach to airway management during out-of-hospital cardiac arrest (OHCA) is unknown.

Objective: To determine whether a supraglottic airway device (SGA) is superior to tracheal intubation (TI) as the initial advanced airway management (AAM) strategy in adults with non-traumatic OHCA.

Design, Setting and Participants: Cluster randomized trial of emergency medical services clinicians (paramedics) from four ambulance services in England covering approximately 21 million people. Patients ≥18 years old, who had a non-traumatic OHCA and were attended by a participating paramedic, were enrolled automatically under a waiver of consent between June 2015 and August 2017. Follow-up ended in February 2018.

Intervention: Paramedics were randomised 1:1 to use TI (764 paramedics) or SGA (759 paramedics) for their initial AAM.

Main Outcome Measures: Primary outcome was modified Rankin Scale (mRS) at hospital discharge or 30 days after OHCA, whichever occurred sooner. mRS was dichotomised; 0-3 (good outcome) or 4-6 (poor outcome; 6=death). Secondary outcomes included ventilation success, regurgitation and aspiration.

Results: 9,296 eligible patients (SGA group: 4,886, TI group, 4,410) were enrolled (median age 73 years; 3,373, 36.3% women), and mRS was known for 9,289. Characteristics were similar between groups. 6.4% (311/4882) of patients in the SGA group and 6.8% (300/4407) of patients in the TI group had a good outcome (adjusted risk difference (RD): -0.6%; 95%CI -1.6% to +0.4%). Ventilation success was higher in the SGA strategy group (SGA: 87.4%;

4255/4868. TI: 79.0%; 3473/4397; adjusted RD: +8.3%; 95%CI +6.3% to +10.2%), however patients allocated to TI were less likely to receive AAM (SGA: 85.2%; 4,161/4883. TI: 77.6%; 3,419/4404). Regurgitation and aspiration were not significantly different (regurgitation: SGA, 26.1%, 1268/4865; TI, 24.5%, 1072/4372; adjusted RD =+1.4% 95%CI -0.6% to +3.4%; aspiration: SGA, 15.1%, 729/4824; TI, 14.9%, 647/4337; adjusted RD=+0.1%, 95%CI -1.5% to +1.8%).

Conclusions and Relevance: Among patients with OHCA, randomization to a strategy of advanced airway management with a supraglottic airway device compared with tracheal intubation did not result in a favorable functional outcome at 30 days.

Trial Registration: ISRCTN No: 08256118.

Introduction

Out-of-hospital cardiac arrest (OHCA) is common, sudden and often fatal. In England during 2014, Emergency Medical Services (EMS) attempted resuscitation in almost 30,000 people; only 25% achieved a return of spontaneous circulation (ROSC), and 8% were discharged from hospital alive.[1] During OHCA few advanced life support (ALS) therapies have been shown to improve outcome.[2] This is partly due to uncertainty about effective treatments, and partly because it is challenging to conduct high-quality randomized clinical trials (RCTs) in patients with OHCA. Consequently, many current clinical recommendations are based on observational studies and expert consensus.[3]

Optimal airway management during OHCA is a key area of uncertainty, with very little high-quality research on which to base treatment recommendations.[4] Options range from basic or minimal airway intervention to early advanced procedures that require training and expertise.

The advanced procedure of tracheal intubation (TI) has been considered a definitive airway management technique.[5] However, large observational studies (>100,000 patients) have consistently favored basic airway management, e.g. bag-mask ventilation, over TI.[6,7] The introduction of supraglottic airways (SGAs) offers an alternative advanced airway management (AAM) technique during OHCA. Insertion of a SGA is simpler and faster than TI,[8] and proficiency requires less training and ongoing practice.[9] Observational evidence has suggested a possible survival advantage for TI over SGAs.[10] However, a large-scale RCT is required to identify the optimal approach to AAM during OHCA.

The objective of this trial was to estimate the difference in modified Rankin Scale (mRS) at hospital discharge or 30 days post OHCA, if sooner, between groups of patients managed by paramedics randomized to use either SGA or TI as their initial advanced airway management strategy following OHCA.

Methods

Study Design

The protocol and statistical analysis plan (SAP) for this parallel two-group multi-center cluster-RCT are included in the online supplement, and the protocol has been published.[11]

Paramedic and Patient Population

Paramedics were recruited from four large EMS provider organizations (ambulance services) in England, which cover 21 million people (40% of England's population). The trial population was adults who had a non-traumatic OHCA.

Patient inclusion criteria were: known or believed to be 18 years of age or older; non-traumatic OHCA; attended by a paramedic participating in the trial who was either the first or second paramedic to arrive at the patient's side; resuscitation commenced or continued by EMS clinicians. Patient exclusion criteria were: detained in the Prison Service; previously recruited to the trial (determined retrospectively); resuscitation deemed inappropriate (using guidelines based on those of the Joint Royal Colleges Ambulance Liaison Committee[12]); advanced airway already in place (inserted by another paramedic, doctor or nurse) when a paramedic participating in the trial arrived at the patient's side; known to be already enrolled in another pre-hospital RCT; patient mouth opening <2 cm.

Paramedics could not be blinded to their allocation and mechanisms were required to avoid the risk of differential recruitment by paramedics based on the patient's perceived likely outcome. Therefore, every eligible patient attended by a participating paramedic was automatically enrolled in the study under a waiver of consent provided by the Confidentiality Advisory Group (CAG: reference 14/CAG/1030). Ethics review and approval was provided

by South Central - Oxford C Research Ethics Committee (REC: reference 14/SC/1219), which included a process of written informed consent for participating paramedics. A disadvantage of automatic enrolment was that enrolled patients might not follow the study protocol because the enrolling paramedic could not recall the protocol details (attendance at an OHCA is relatively rare and stressful for paramedics), or the paramedic mistakenly believed the patient to be ineligible.

Randomization

Because OHCA requires immediate treatment, randomizing patients at the point of OHCA was considered impractical. Therefore, paramedics were randomized to use one of the two AAM strategies for all eligible patients that they attended. This design, although clustered, created many clusters with a small average number of patients, minimising the effect of intra-cluster correlation and the risk of chance imbalances between groups.

Paramedics were randomised in a 1:1 ratio using a purpose-designed secure internet-based system. The random sequence was computer generated in advance using varying block sizes (range 4-8) and stratified by EMS provider organization (4 levels), paramedic experience (2 levels) and distance from the paramedic's base ambulance station to the usual destination hospital (2 levels).

Intervention

The intervention was the insertion of a second generation SGA with a soft non-inflatable cuff (i-gel: Intersurgical, Wokingham, UK). Because of its speed and ease of insertion, this device has become the most commonly used SGA during OHCA in England.[13,14] The current standard care pathway is TI using direct laryngoscopy; videolaryngoscopy is not used by paramedics in England. A standard approach to airway management, from basic to

advanced techniques, was agreed by participating ambulance services. This included the use of bag-mask ventilation (BMV) and simple airway adjuncts prior to AAM. Care proceeded as usual for patients with OHCA enrolled in the trial, apart from the initial AAM. All other care was delivered according to standard international resuscitation guidelines.[3]

Participating paramedics received additional training in their allocated AAM intervention immediately after randomization. Training comprised theoretical and simulation-based practice over 1 hour with a brief assessment to confirm competence. For TI a two-person technique using an intubating bougie was recommended. End tidal carbon dioxide monitoring was used to confirm correct device placement in all patients.

Protocol deviations could arise because paramedics have both strategies available to them. Usual practice follows a “step-wise” approach from simple to more advanced techniques, but paramedics have clinical freedom to adapt airway management during OHCA to the patient’s anatomy, position and perceived needs. The trial protocol specified two attempts using the allocated strategy before proceeding to the alternative, but paramedics had discretion to deviate from the protocol on clinical grounds. Allowing discretion was necessary to avoid a paramedic feeling obliged to undertake an intervention that they believed to be against the patient’s best interests. This was also necessary to secure REC approval and professional support.

Outcomes

The primary outcome was modified Rankin Scale (mRS) at hospital discharge, or at 30 days if the patient remained in hospital. Patients were conveyed to and followed up in hospital where mRS was collected by assessors blinded to treatment allocation. mRS is used widely in OHCA research,[15,16] and is usually dichotomised as good (0-3) or poor outcome/death (4-6; 6 indicates death). The following secondary outcomes were collected for all eligible

patients, with all but the last 2 reported by participating paramedics: initial ventilation success, defined as visible chest rise (classified as “yes” when AAM was not used); regurgitation (stomach contents visible in the mouth or nose) and aspiration (stomach contents visible below the vocal cords or inside a correctly placed tracheal tube or airway channel of a SGA) (each classified as “no” when AAM was not used); loss of a previously established airway (patients with AAM only); sequence of airway interventions delivered (patients with AAM only); ROSC (i. patients with AAM only for ROSC during airway management; ii. patients who died at the scene classified as “no” for ROSC at hospital admission); airway management in place when ROSC was achieved, or resuscitation was discontinued (patients with AAM only); chest compression fraction (in a sub-set of patients in two EMS provider organizations); time to death.

Good quality, continuous CPR is associated with increased survival and improved function following OHCA, and the concept of compression fraction has been developed to standardise its measurement.[17] Compression fraction was therefore measured and compared in a sub-set of patients in two ambulance services using the “CPR Card” (Laerdal; Stavanger, Norway), a small disposable device placed in the centre of the patient’s chest during CPR. The device gives no feedback to the user but records data that can be retrieved subsequently.

Resource use to support a cost effectiveness analysis and longer-term function were also collected. These data will be reported separately.

Sample Size

In a previous feasibility study, 9% of patients survived to hospital discharge.[18] No data were available for mRS. However, death and poor functional outcome after OHCA are closely related because death is the most common outcome.[16] A 2% improvement in the proportion

of patients achieving a good outcome (mRS 0-3) was judged to be clinically important, and consistent with the 2.4% difference in survival to hospital discharge between TI and SGAs observed in retrospective data.[19] This meant that 9,070 patients in total were needed to detect a difference of 8% vs 10% at the 5% significance level and 90% power, after allowing for clustering.[11]

Statistical Analysis

Analysis of the primary outcome, and exploratory analyses of secondary outcomes, were performed according to a pre-specified statistical analysis plan (SAP), which was finalised before data lock and any comparative analysis, but after the end of recruitment due to staff changes in the statistical team. Some typographical errors were corrected in version 2 and some points were clarified, but no substantive changes were made. No comparative post-hoc analyses were performed.

The primary analyses included all eligible patients with outcome data available (Tables report details), except for the following secondary outcomes which only applied to those who received AAM: loss of a previously established airway; ROSC during airway management; airway management in place when ROSC was achieved or resuscitation was discontinued. Chest compression fraction was only measured in small subset of patients. Patients were grouped by the allocation of the first participating paramedic on scene (main analyses). Analyses were adjusted for stratification factors as fixed effects. For binary outcomes, mixed-effects logistic regression estimated odds ratios for the primary analysis, with paramedic fitted as a random effect. Risk differences and risk ratios were also estimated using generalised linear regression, with standard errors calculated using a sandwich estimator to allow for clustering. Risk ratios are reported in the Supplement (eTable 7). For time-to-event outcomes, Cox proportional-hazards regression was used. The proportionality assumption, checked using Schoenfeld residuals, was met.

The level of missing data is given in footnotes to the Tables. Multiple imputation was not considered as the level of missing data was 7 patients (0.08%) for the primary outcome and less than 1.5% for all but one secondary outcome which had 6.4% missing data.

Two pre-specified exploratory sub-group analyses were performed for the primary outcome; i) Utstein comparator group (OHCA with a likely cardiac cause that is witnessed and has an initial rhythm amenable to defibrillation[20]) versus non-comparator group, and ii) OHCA witnessed by EMS clinician or not. The treatment effect in sub-groups was compared by testing for an interaction between paramedic allocation and the sub-group variable.

Three pre-specified exploratory sensitivity analyses were performed for the primary outcome. The first extended the population to include patients attended by a participating paramedic who were not resuscitated (i.e. trial patients plus non-resuscitated patients). This was prompted by feedback from a pre-planned closed interim analysis of half the sample considered by the Data Monitoring and Safety Committee. The second and third sensitivity analyses, restricted to the cohort of patients who received AAM (as allocated and treatment received comparisons), were planned from the outset.

A 5% significance level (two-sided) was used. Groups were compared using Wald tests. No adjustment was made for multiple testing, so that secondary endpoints should be considered exploratory [21]. All analyses were performed using Stata version 15.1 (StataCorp).

Results

Participants, Baseline Characteristics and Protocol Adherence

Overall, 1,523 paramedics were recruited and randomized. Of 13,462 potentially eligible patients attended by a participating paramedic between June 2015 and August 2017, 4,166 (31%) were excluded and 9,296 (69%) were enrolled (Figure 1). Enrolled patients were conveyed to 95 hospitals and followed-up to hospital discharge. Paramedics' allocation was balanced (SGA: 759; TI: 764), but there were more patients in the SGA (n=4,886) than the TI group (n=4,410). The proportions of patients with OHCA resuscitated (SGA: 51.6%, 7007/13587; TI: 50.5%, 6455/12789) and eligible (SGA; 69.7%, 4886/7006; TI: 68.3%; 4410/6454) were similar in the two groups.

Patient characteristics and cardiac arrest details were balanced between the two groups (Table 1; eTables 1 and 2).

Fewer patients allocated to TI received AAM (77.6%; 3,419/4404, vs. 85.2%; 4,161/4883). TI patients were also more likely to crossover to SGA as a result of clinical decision-making by the paramedic on scene (Figure 2; eFigure 1, eTable 3).

Primary Outcome

Primary outcome data were available for 99.9% (9,289/9,296) of patients (Table 2); 6.4% (311/4882) in the SGA group and 6.8% (300/4407) in the TI group had a good outcome (mRS 0-3, odds ratio (OR) 0.918, 95% confidence interval (95%CI) 0.77-1.09; risk difference (RD, SGA minus TI) -0.6%, 95%CI -1.6% to +0.4%; Figure 3 and eFigure 2).

Exploratory Sensitivity Analyses

Including patients attended by a participating paramedic who were not resuscitated did not change the conclusion (SGA, 2.7%, 311/11462; TI, 2.8%, 300/10741; OR=0.959; 95%CI: 0.81-1.14. RD=-0.2%; 95%CI -0.6% to +0.3%; Figure 3, eTable 4). However, in the 7,576 (81%) patients who received AAM more patients in the SGA group had a good outcome (SGA, 3.9%, 163/4158; TI, 2.6%, 88/3418; OR=1.57, 95%CI 1.18-2.07; RD=+1.4%; 95%CI +0.5% to +2.2%). This effect was also observed in the analysis with patients grouped according to the first AAM intervention received (SGA, 4.2%, 193/4630; TI, 2.0%, 58/2838; OR=2.06, 95%CI 1.51-2.81; RD=+2.1%, 95%CI +1.2% to +2.9%).

Exploratory Subgroup Analyses

There was no interaction between allocation and either subgroup (Figure 3; Utstein comparator group vs not, p=0.24; cardiac arrest witnessed by EMS clinician vs not, p=0.24).

Secondary Outcomes

Secondary outcomes are shown in Table 2 and eTable 5. The SGA treatment strategy was significantly more successful in achieving ventilation after up to two attempts (SGA, 87.4%, 4255/4868; TI, 79.0%, 3473/4397; OR=1.92, 95%CI 1.66-2.22; RD=+2.1%, 95%CI +1.2% to +2.9%). Regurgitation and aspiration at any time (i.e. before and/or after AMM) were similar (regurgitation: SGA, 26.1%, 1268/4865; TI, 24.5%, 1072/4372; OR=1.08, 95%CI 0.96-1.20; RD =+1.4% 95%CI -0.6% to +3.4%; aspiration: SGA, 15.1%, 729/4824; TI, 14.9%, 647/4337; OR=1.01, 95%CI 0.88-1.16; RD=+0.1%, 95%CI -1.5% to +1.8%).

The median time to death was not significantly different between the two groups (SGA: 67 minutes, n=4871. TI: 63 minutes, n=4400), and neither was the compression fraction in a

very small sample of 66 patients (SGA, median 86%, IQR 81-91%, n=34; TI, median 83%, IQR 74%-89%, n=32; p=0.14; eTable 6).

Discussion

In this pragmatic cluster RCT no significant difference was found between TI and SGA in the primary outcome of good outcome after OHCA for all trial patients.

Patients with a short duration of cardiac arrest and who receive bystander resuscitation and/or defibrillation are considerably more likely to survive and are also less likely to require AAM.[22] This problem of confounding by indication is an important limitation of many large observational studies that show an association between AAM and poor outcome in OHCA.[23] This study found that 21.1% (360/1704) of patients who received no AAM achieved a good outcome compared to 3.3% (251/7576) of patients who received AAM.

Paramedics allocated to TI were less likely to use AAM than paramedics allocated to SGA. TI is a more complex skill than SGA insertion and requires two practitioners, additional equipment and good access to the patient's airway,[24] yet OHCA often occurs in locations where patient access is challenging. TI has been associated with potential harms including unrecognised oesophageal intubation, lengthy pauses in chest compressions and over-ventilation.[25,26] No evidence of a difference in compression fraction was found in a small sub-sample of enrolled patients, but the potential for harm associated with TI persists.

At the outset, it was expected that most patients with a favourable outcome would not receive AAM, and that some crossover would occur. For these reasons, two exploratory sensitivity analyses were pre-specified only in patients who received AAM, even though these analyses are susceptible to bias.[27] Patients who received AAM were similar in the two groups (eTable 1; eTable 2), and a strategy of SGA first was associated with better outcomes whenever AAM was undertaken by a trial paramedic (eTable 4), but the difference between groups was less than the pre-specified clinically important 2% difference and less than the minimal important difference of approximately 3% reported by others.[28] The SGA first strategy also achieved initial ventilation success more often, although regurgitation and

aspiration during or after AAM were significantly more common in the SGA group. Conversely, patients in the TI group were significantly more likely to regurgitate and aspirate before AAM, possibly due to less frequent use of advanced techniques to secure the airway in this group and the increased time required for TI compared to insertion of a SGA.

A recent RCT of French and Belgian patients with OHCA, comparing BMV with TI delivered by physicians as part of an EMS team, proved inconclusive.[29] To our knowledge, no RCT has compared BMV with an SGA in patients with OHCA. Reported rates of ventilation and TI success have been higher in previous studies,[29,30,31] but these have been based on selected populations and practitioners with greater training and experience, including physicians. This study reflects both the reality of current paramedic practice in England, and the challenges of airway management in a patient group where regurgitation and poor airway access are common.

Loss of a previously established airway occurred twice as frequently in the SGA group than in the TI group. There are some cardiac arrest patients for whom effective ventilation cannot be achieved with basic airway management techniques or an SGA, and for whom TI may be the only way of achieving effective ventilation. The exact role of different advanced airway management techniques in adults with OHCA, and the associated implications for skill acquisition and maintenance, remain to be determined.

Limitations

This study has several limitations. First, the trial population included patients who did and did not receive AAM, and the use of AAM was greater among paramedics in the SGA group compared to those in the TI group which could result in confounding by indication.[32] Second, there was an imbalance in the number of patients in the two groups, probably due to unequal distribution of high-recruiting paramedics in the two groups; it was not possible to stratify for

this because high-recruiting paramedics could not be identified in advance. Third, there was crossover between groups, which was inevitable on practical and ethical grounds. Fourth, although other elements of care (e.g. initial basic airway management and subsequent on-scene and in-hospital care, such as targeted temperature management and access to angiography) followed established guidelines, differences in these factors between groups could have influenced the findings. Fifth, the participating paramedics were volunteers, and their airway skills may not be representative of those who chose not to take part. Sixth, the findings are applicable to use of the trial SGA in countries with similar EMS provision to England, where paramedics attend most OHCAs. The findings may not be applicable in countries with physician-led EMS provision or to other SGAs which may have different characteristics. However, the principles underpinning the insertion and function of all SGAs are similar.

Conclusions

Among patients with OHCA, randomization to a strategy of advanced airway management with a supraglottic airway device compared with tracheal intubation did not result in a favorable functional outcome at 30 days.

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Author Contributions:

Guarantors: Benger and Rogers had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, and interpretation of data: All authors.

Drafting of the manuscript: Benger.

Critical revision of the manuscript for important intellectual content: All authors.

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Supplementary Data:

Supplementary data associated with this article can be found online

Table 1: Patient demography and cardiac arrest details

All trial patients	Randomised to TI (n=4,410)		Randomised to Trial SGA (n=4,886)	
	n	%	n	%
DEMOGRAPHY				
Male gender	2791/4410	63.3%	3132/4886	64.1%
Age (median, IQR)	74	(62, 83)	73	(61, 82)
INITIAL CARDIAC ARREST DETAILS				
Time from 999 call to first EMS clinician arrival (mins; median, IQR)	8	(5, 11)	7	(5, 11)
Time from first EMS clinician arrival to trial EMS clinician arrival (mins; median, IQR)[1]	0	(0, 4)	1	(0, 4)
Presenting rhythm				
Asystole	2356/4316	54.6%	2597/4791	54.2%
VF	979/4316	22.7%	1094/4791	22.8%
Pulseless VT	44/4316	1.0%	39/4791	0.8%
PEA	937/4316	21.7%	1061/4791	22.1%
Arrest witnessed	2788/4407	63.3%	3101/4883	63.5%
By bystander	2231/2788	80.0%	2493/3100	80.4%
By EMS clinician	557/2788	20.0%	607/3100	19.6%
Bystander/responder CPR before EMS clinician arrival	2774/4406	63.0%	3149/4883	64.5%
Bystander/responder defibrillation before EMS clinician arrival[2]	146/4390	3.3%	176/4863	3.6%
If yes, ROSC achieved	20/146	13.7%	27/176	15.3%
ON ARRIVAL OF STUDY EMS CLINICIAN				
Airway management in progress	1384/4389	31.5%	1463/4863	30.1%
BVM only	273/1383	19.7%	307/1463	21.0%
OPA and BVM	766/1383	55.4%	875/1463	59.8%
NPA and BVM	11/1383	0.8%	11/1463	0.8%
Trial SGA	262/1383	18.9%	190/1463	13.0%
Intubation	3/1383	0.2%	3/1463	0.2%
Other SGA	44/1383	3.2%	57/1463	3.9%
Mouth to mouth	8/1383	0.6%	10/1463	0.7%
Face shield/pocket mask	5/1383	0.4%	4/1463	0.3%
Suction	3/1383	0.2%	2/1463	0.1%
Other	8/1383	0.6%	4/1463	0.3%
Successful ventilations ongoing	1110/1372	80.9%	1154/1455	79.3%
Patient had ROSC on arrival	300/4393	6.8%	328/4862	6.8%

TI=Tracheal Intubation, SGA=Supraglottic Airway, IQR=Interquartile range, VF=Ventricular Fibrillation, VT=Ventricular Tachycardia, PEA=Pulseless Electrical Activity, EMS=Emergency Medical Services, CPR=Cardiopulmonary Resuscitation, ROSC=Return of Spontaneous Circulation, BVM=Bag Valve Mask, OPA=Oropharyngeal Airway, NPA=Nasopharyngeal Airway.

Missing data (randomised to TI, randomised to trial SGA): [1]4 patients (3, 1).

[2]Where bystander/responder defibrillation occurred before EMS clinician arrival this was achieved using an automated external defibrillator (AED) available at scene.

All patients are grouped by the allocation of the first study EMS clinician on scene.

Table 2: Primary outcome (modified Rankin Scale at hospital discharge/30 days), survival status and main secondary outcomes

All trial patients	Randomised to TI (n=4,410) n	%	Randomised to Trial SGA (n=4,886) n	%	Estimate (95% CI)	p-value	ICC	Risk difference estimate (95% CI)	p-value
PRIMARY OUTCOME									
mRS (0 to 3; good recovery)	300/4407	6.8%	311/4882	6.4%	OR=0.92 (0.77, 1.09)	0.33	0.05	RD=-0.006 (-0.016, 0.004)	0.24
0 (no symptoms)	124/4407	2.8%	117/4882	2.4%					
1	48/4407	1.1%	41/4882	0.8%					
2	50/4407	1.1%	58/4882	1.2%					
3	78/4407	1.8%	95/4882	1.9%					
4	46/4407	1.0%	45/4882	0.9%					
5	27/4407	0.6%	39/4882	0.8%					
6 (deceased)	4034/4407	91.5%	4487/4882	91.9%					
SECONDARY OUTCOMES									
Survival status:									
Died at scene	2488/4407	56.5%	2623/4882	53.7%					
Died prior to ICU admission	1058/4407	24.0%	1226/4882	25.1%					
Died prior to ICU discharge	369/4407	8.4%	503/4882	10.3%					
Died prior to hospital discharge	120/4407	2.7%	138/4882	2.8%					
Survived to 30 days/hospital discharge	372/4407	8.4%	392/4882	8.0%					
Time to death (minutes; median, IQR, n) [1]	63 (41,216)	4400	67 (41, 267)	4871	HR=0.97 (0.93, 1.02)	0.22			
Time to death 0-72 hours (minutes; n, median, IQR) [1]	63 (41,205)	4400	67 (41, 246)	4871	HR=0.96 (0.92, 1.00)	0.07			
72 hour survival	575/4395	13.1%	664/4872	13.6%	OR=1.04 (0.92, 1.18)	0.54	0.02	RD=0.004 (-0.010, 0.019)	0.54
Initial ventilation success (up to two attempts at AAM)	3473/4397	79.0%	4255/4868	87.4%	OR=1.92 (1.66, 2.22)	<0.001	0.12	RD=0.083 (0.063, 0.102)	<0.001
TI	1891/2723	69.4%	92/116	79.3%					
Trial SGA	542/617	87.8%	3412/3994	85.4%					
Other SGA	55/72	76.4%	29/36	80.6%					

All trial patients	Randomised to TI (n=4,410)		Randomised to Trial SGA (n=4,886)		Estimate (95% CI)	p-value	ICC	Risk difference estimate (95% CI)	p-value
	n	%	n	%					
Any loss of a previously established airway[2]	153/3081	5.0%	412/3900	10.6%	OR=2.29 (1.86, 2.82)	<0.001	0.07	RD=0.059 (0.046, 0.072)	<0.001
TI	70/2149	3.3%	33/570	5.8%					
Trial SGA	84/981	8.6%	389/3455	11.3%					
Other SGA	5/171	2.9%	3/33	9.1%					
Regurgitation at any time	1072/4372	24.5%	1268/4865	26.1%	OR=1.08 (0.96, 1.20)	0.21	0.06	RD=0.014 (-0.006, 0.034)	0.17
Aspiration at any time	647/4337	14.9%	729/4824	15.1%	OR=1.01 (0.88, 1.16)	0.84	0.08	RD=0.001 (-0.015, 0.018)	0.86
Regurgitation before initial SGA/TI attempt	923/4379	21.1%	846/4869	17.4%					
Aspiration before initial SGA/TI attempt	589/4355	13.5%	532/4840	11.0%					
Regurgitation during or after initial SGA/TI attempt	543/4361	12.5%	875/4857	18.0%					
Aspiration during or after initial SGA/TI attempt	304/4344	7.0%	473/4829	9.8%					
Admitted to ED/hospital	1922/4410	43.6%	2263/4886	46.3%					
ROSC on ED/hospital arrival	1249/4404	28.4%	1495/4880	30.6%	OR=1.12 (1.02, 1.23)	0.02	0.01	RD=0.022 (0.003, 0.042)	0.03
Survived to ED discharge	861/1919	44.9%	1033/2259	45.7%					

TI=Tracheal Intubation, SGA=Supraglottic Airway device, CI=Confidence Interval, ICC=Intracluster correlation coefficient, OR=odds ratio, RD=risk difference, HR=Hazard ratio, mRS=modified Rankin Scale score, ICU=Intensive Care Unit, IQR=Interquartile Range, AAM=advanced airway management, ED=Emergency department, ROSC=Return of spontaneous circulation, EMS=Emergency medical services.

Note:

Odds ratios and risk differences are adjusted for stratification factors fitted as fixed effects. Odds ratios were obtained from a mixed effects logistic regression model with study EMS clinician fitted as a random effect. Risk differences were obtained by fitting a generalised linear model (binomial family and identity link) with standard errors adjusted for clustering. The hazard ratios are adjusted for EMS clinician experience and distance from usual hospital and stratified by EMS provider organisation with standard errors adjusted for clustering. Wald p-values are displayed.

[1] *Patients who survived to ICU discharge but did not consent to active or passive follow-up were censored at ICU discharge because research approvals did not permit analysis of subsequent data, apart from the mRS.*

[2] *Trial patients with at least one AAM attempt only*

All patients are grouped by the allocation of the first study EMS clinician on scene.

Figure 1 Flow of study EMS clinicians and patients

Submitted separately.

Figure 2 Interventions received and patient outcome by study allocation

Submitted separately.

Figure 3 Forest plot of primary outcome results (mRS at hospital discharge/30 days)

Submitted separately, notes for figure below

mRS=Modified Rankin Scale, TI=Tracheal Intubation, SGA=Supraglottic Airway device, OR=Odds Ratio, CI=Confidence Interval, EMS=Emergency Medical Services.
Odds ratios are estimated from a mixed effects logistic regression model, with stratification factors fitted as fixed effects and study EMS clinician as a random effect). Wald p-values are displayed.
The size of the point estimate (grey dot) is proportional to the number of patients included
Note:
Patients are grouped by the allocation of the first study EMS clinician on scene.
eFigure 2 displays the breakdown of the mRS scores in the form of horizontally stacked bar charts.
n/N is displayed where n is the number of patients with a score of 0-3 (good recovery) and N is the total number in that group.
[1] *All trial patients.*
[2] *All trial patients. Patients whose cardiac arrest was recorded as not witnessed are included in the Utstein non-comparator group*
[3] All trial patients. Patients whose cardiac arrest was recorded as not witnessed are included in the not witnessed by ambulance staff group
[4] *All trial patients plus patients attended by a study EMS clinician who were not resuscitated.*
Missing data (randomised to TI, randomised to SGA): [1] *7 patients (3, 4).* [2] *103 patients (52, 51).* [3] *7 patients (3, 4).* [4] *4 patients (1, 3).*