Association of Advanced Airway Insertion Timing and Outcomes After Out-of-Hospital Cardiac Arrest

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Study objective: While often prioritized in the resuscitation of patients with out-of-hospital cardiac arrest, the optimal timing of advanced airway insertion is unknown. We evaluated the association between the timing of advanced airway (laryngeal tube and endotracheal intubation) insertion attempt and survival to hospital discharge in adult out-of-hospital cardiac arrest.

Methods: We performed a secondary analysis of the Pragmatic Airway Resuscitation Trial (PART), a clinical trial comparing the effects of laryngeal tube and endotracheal intubation on outcomes after adult out-of-hospital cardiac arrest. We stratified the cohort by randomized airway strategy (laryngeal tube or endotracheal intubation). Within each subset, we defined a time-dependent propensity score using patients, arrest, and emergency medical services systems characteristics. Using the propensity score, we matched each patient receiving an initial attempt of laryngeal tube or endotracheal intubation with a patient at risk of receiving laryngeal tube or endotracheal intubation attempt within the same minute.

Results: Of 2,146 eligible patients, 1,091 (50.8%) and 1,055 (49.2%) were assigned to initial laryngeal tube and endotracheal intubation strategies, respectively. In the propensity score-matched cohort, timing of laryngeal tube insertion attempt was not associated with survival to hospital discharge: 0 to lesser than 5 minutes (risk ratio [RR]=1.35, 95% confidence interval [CI] 0.53 to 3.44); 5 to lesser than10 minutes (RR=1.07, 95% CI 0.66 to 1.73); 10 to lesser than 15 minutes (RR=1.17, 95% CI 0.60 to 2.31); or 15 to lesser than 20 minutes (RR=2.09, 95% CI 0.35 to 12.47) after advanced life support arrival. Timing of endotracheal intubation attempt was also not associated with survival: 0 to lesser than 5 minutes (RR=0.50, 95% CI 0.05 to 4.87); 5 to lesser than10 minutes (RR=1.20, 95% CI 0.51 to 2.81); 10 to lesser than15 minutes (RR=1.03, 95% CI 0.49 to 2.14); 15 to lesser than 20 minutes (RR=0.85, 95% CI 0.30 to 2.42); or more than/equal to 20 minutes (RR=0.71, 95% CI 0.07 to 7.14).

Conclusion: In the PART, timing of advanced airway insertion attempt was not associated with survival to hospital discharge. [Ann Emerg Med. 2021;■:1-14.]

Please see page XX for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Out-of-hospital cardiac arrest is a major public health problem, annually affecting over 356,000 individuals in the United States, with a high mortality rate.[1] For patients with out-of-hospital cardiac arrest, emergency medical services (EMS) provide initial medical care as a part of the "chain of survival."[2] In the United States, EMS clinicians commonly perform advanced airway management with supraglottic airway (eg, laryngeal tube) or endotracheal intubation.[3,4] Recently, the Pragmatic Airway Resuscitation Trial (PART) compared the effects of an initial laryngeal tube strategy versus an initial endotracheal intubation strategy for adult patients with out-of-hospital cardiac arrest. The trial found better outcomes with a strategy of initial laryngeal tube compared with initial endotracheal intubation.[5]

Importance

The ideal time for advanced airway insertion is unclear. While early advanced airway insertion may facilitate earlier optimal oxygen delivery, airway insertion and positive pressure ventilation may also adversely influence the quality of concurrent chest compressions or impair venous return by increasing intrathoracic pressure.[6-8] Evaluation of the

Editor's Capsule Summary

What is already known on this topic

The ideal time for advanced airway management in out-of-hospital cardiac arrest is unclear.

What question this study addressed.

Does survival differ between patients who receive their laryngeal or endotracheal tubes early versus late in their resuscitation?

What this study adds to our knowledge

In this propensity-scored secondary analysis of a prospective trial of 2,146 adults with out-of-hospital cardiac arrest, there was no survival difference between those whose advanced airway management occurred within 5 minutes, at 5-10 minutes, at 10-15 minutes, or at 15-20 minutes.

How this is relevant to clinical practice

This large observational analysis found no survival advantage associated with early laryngeal or endotracheal tube placement in adult out-of-hospital cardiac arrest.

interplay of timing of advanced airway insertion is important to optimize resuscitation. The International Liaison Committee on Resuscitation's Advanced Life Support Task Force evaluated the scientific evidence of advanced airway management during cardiac arrest in 2019, including PART, but was unable to make recommendations regarding the optimal timing of advanced airway management due to limitations in the published literature.[9]

Goals of This Investigation

Our objective was to evaluate the association between the timing of initial advanced airway insertion and patient outcomes after out-of-hospital cardiac arrest in PART.

METHODS

Study Design and Setting

We performed a retrospective secondary analysis of clinical data from the PART. The methods and results of PART have been previously reported.[5,10] Briefly, PART was a cluster randomized controlled trial encompassing 27 EMS agencies in the United States. The trial compared the effectiveness of a strategy of initial laryngeal tube insertion versus initial endotracheal intubation in adult patients with out-of-hospital cardiac arrest requiring bag-valve-mask ventilation.[5,10] PART enrolled 3,004 patients from December 2015 and November 2017.[5] The institutional review boards of the participating institutions approved the PART study under federal rules for conduct of emergency research under exception from informed consent (21 CFR 50.24). In the PART, key time variables in our study (eg, start time of advanced airway insertion and time of successful airway placement) were required data and prospectively collected by EMS clinicians with an instruction to use a record button of a defibrillator. Prior to the initiation of the PART, all participating EMS agencies received EMS protocol training. The training reviewed the standardized definitions and reporting practices for the required data. The present analysis of deidentified data was deemed exempt from regulations related to human subject research by the University of Pittsburgh's institutional review board.

Selection of Participants

We included patients who had been enrolled in PART, which included adults (presumed or known to be $\geq$18 years old) with nontraumatic out-of-hospital cardiac arrest treated by participating EMS agencies and requiring anticipated ventilatory support or advanced airway management.[5,10] Exclusion criteria in PART included known pregnancy, known prisoners, traumatic arrest etiology, major bleeding or exsanguination, advanced airway insertion prior to participating EMS agency arrival, and preexisting tracheostomy.[5] In this secondary analysis, we further excluded patients with EMS-witnessed out-of-hospital cardiac arrest, unknown age, unknown time of advanced life support EMS arrival, unknown time of the first laryngeal tube or endotracheal intubation attempt, negative value in an interval between advanced life support arrival and time of the first laryngeal tube or endotracheal intubation attempt, unknown time of time-dependent covariates (shock delivery after advanced life support arrival, epinephrine administration, and departure from the scene), negative values in intervals between advanced life support arrival and the time-dependent covariates, or unknown survival to hospital discharge status. We specifically excluded patients with EMS-witnessed out-of-hospital cardiac arrest since these patients were not at risk of receiving intraarrest advanced airway insertion attempt between advanced life support arrival and time of EMS-witnessed arrest in a survival analysis model to calculate time-dependent propensity score as described below. In the analysis for neurologic outcome, we additionally excluded patients with missing neurologic outcome data.

Exposure

The main exposure was the interval between advanced life support arrival and the first laryngeal tube or endotracheal intubation attempt. The laryngeal tube attempt was defined as an insertion of laryngeal tube between the teeth, and endotracheal intubation attempt was defined as insertion of laryngoscope between the teeth.[5] The interval was defined in whole minutes (ie, laryngeal tube or endotracheal intubation attempt at 0 minutes indicated that the patient received laryngeal tube or endotracheal intubation attempt within the same minute after advanced life support arrival).

Outcomes

The primary outcome of the present analysis was survival to hospital discharge. Secondary outcomes were favorable neurologic status at hospital discharge—defined as modified Rankin scale score $\leq$3—and 72-hour survival.

Resuscitation Time Bias

When timing of an intraarrest intervention (eg, advanced airway insertion) is assessed, it is crucial to account for resuscitation time bias.[11] Patients cannot have return of spontaneous circulation before the intervention due to the way the intraarrest intervention is defined. Therefore, late intervention groups tend to have longer resuscitation duration than early intervention groups. Since longer resuscitation duration is associated with worse outcomes,[12] the late intraarrest intervention is biased toward harmful effects.[11]

Statistical Analysis

We stratified the analysis based on randomized initial airway management strategy (initial laryngeal tube or initial endotracheal intubation). We analyzed the data by intention to treat (ie, protocol deviations and cross-overs remained in their originally assigned groups).

To address potential resuscitation time bias,[11] we used time-dependent propensity score and risk-set matching in each randomized initial airway management strategy cohort.[13-17] We calculated the propensity score as time-varying probability of receiving an attempt of advanced airway insertion at any given minutes after advanced life support arrival. We defined propensity scores separately for each randomized cohort (laryngeal tube or endotracheal intubation) using a competing risk survival regression model. For the laryngeal tube group, we defined time to first laryngeal tube insertion attempt as the dependent variable. For the endotracheal intubation group, we defined time to first endotracheal intubation attempt as the dependent variable. In both cohorts, we included the covariates shown in Table 1. We chose these covariates based on their association with survival from prior knowledge, biologic plausibility, and adequate ascertainment.[18-22] We defined advanced life support arrival on the scene as time=0. We included randomization cluster as a covariate to account for the clustering of patients. Additional methodological details are provided in Appendix E1 (available at http://www.annemergmed.com).

In the laryngeal tube cohort, we performed 1:1 matching of each patient receiving the initial laryngeal tube insertion attempt with a patient who was at risk of receiving laryngeal tube. We matched subjects within the same 1-minute time interval based on the nearest propensity score (ie, risk-set matching) (Figure E1, available at http://www.annemergmed.com).[16,17] At-risk patients therefore included those who received laryngeal tube or endotracheal intubation attempt after the matching and those who did not receive laryngeal tube or endotracheal intubation attempt because matching should not be dependent on future events.[16,17] At-risk patients could have been subsequently matched multiple times as at-risk patients until receiving the first laryngeal tube attempt (matching with replacement).[14,15,23] We set the caliper width for the nearest neighbor matching at 0.2 standard deviations of the propensity scores in the logit scale.[24,25] We repeated the process for the endotracheal intubation cohort. To assess the performance of the risk-set matching, we calculated a standardized difference for each covariate, defining a standardized difference $\leq$0.25 as an indicator of a well-matched balance.[25]

In each matched cohort, we fitted a generalized estimating equations (GEE) model with a log link function.[26] We used GEE to address the potential correlation within pairs of risk-set matching. We used frequency weighting adjustment to account for the number of duplications between patients receiving laryngeal tube or endotracheal intubation and at-risk patients due to the matching with replacement.[25] Using the model, we estimated risk ratios (RRs) with 95% confidence intervals (CIs) to assess the association of advanced airway insertion attempt with each outcome, compared to at risk of receiving advanced airway insertion attempt. We therefore estimated effect size of advanced airway insertion at the time point of matching, compared to advanced airway insertion later or no advanced airway insertion.

To evaluate the timing effect of advanced airway insertion attempt, we fitted 2 GEE models with a log link function. One model treated the timing of advanced airway insertion attempt after advanced life support arrival as a categorical variable by 5-minute intervals. The other model

Table 1. Patient characteristics in randomized advanced airway management strategy.

Variable	Randomized to an Initial Laryngeal Tube Strategy (n=1091)	Randomized to an Initial Endotracheal Intubation Strategy (n=1055)
Age, median (IQR), y	64 (52-76)	63 (51-75)
Male, n (%)	687 (63.0)	637 (60.4)
Race, n (%)		
White	616 (56.5)	558 (52.9)
Non-White	257 (23.6)	323 (30.6)
Unknown	218 (20.0)	174 (16.5)
First recorded rhythm, n (%)		
Shockable	232 (21.3)	209 (19.8)
Nonshockable	827 (75.8)	823 (78.0)
Unknown	32 (2.9)	23 (2.2)
Location, n (%)		
Street/highway	24 (2.2)	33 (3.1)
Public building	12 (1.1)	11 (1.0)
Place of recreation	4 (0.4)	8 (0.8)
Industrial place	3 (0.3)	8 (0.8)
Home	780 (71.5)	720 (68.2)
Health care facility	47 (4.3)	41 (3.9)
Residential institution	140 (12.8)	152 (14.4)
Other public property	76 (7.0)	78 (7.4)
Other non-public property	1 (0.1)	3 (0.3)
Unknown	4 (0.4)	1 (0.1)
Witnessed collapse, n (%)		
Bystander	410 (37.6)	418 (39.6)
Unwitness	556 (51.0)	556 (52.7)
Unknown	125 (11.5)	81 (7.7)
Bystander CPR, n (%)	591 (54.2)	600 (56.9)
Bystander AED shock delivery, n (%)	27 (2.5)	32 (3.0)
EMS shock delivery before advanced life support arrival, n (%)	22 (2.0)	22 (2.1)
EMS response time (interval between dispatch and first EMS arrival), median (IQR), minutes	5 (4-6)	5 (4-7)
Interval between dispatch and advanced life support arrival, median (IQR), minutes	5 (4-7)	6 (5-8)
Shock delivery after advanced life support arrival, n (%)	330 (30.2)	290 (27.5)
Epinephrine administration, n (%)	1011 (92.7)	985 (93.4)
Departure from the scene, n (%)	592 (54.3)	555 (52.6)
Randomization cluster		
A	16 (1.5)	41 (3.9)
B	12 (1.1)	9 (0.9)
C	198 (18.1)	297 (28.2)
D	31 (2.8)	30 (2.8)
E	67 (6.1)	50 (4.7)
F	99 (9.1)	76 (7.2)
G	237 (21.7)	223 (21.1)
H	128 (11.7)	95 (9.0)
I	37 (3.4)	22 (2.1)
J	18 (1.6)	34 (3.2)
K	1 (0.1)	7 (0.7)
L	192 (17.6)	119 (11.3)
M	55 (5.0)	52 (4.9)

AED, Automated external defibrillator; *CPR,* cardiopulmonary resuscitation.

treated the timing of advanced airway insertion attempt as a continuous variable and included an interaction term between the advanced airway insertion attempt and time to matching (ie, time from advanced life support arrival to the time of matching [time of advanced airway insertion attempt for those who were matched as receiving advance airway insertion attempt]) in order to evaluate the timing effect of advanced airway insertion attempt. We regarded a significant *P*-value of the interaction as indicating significant timing effect of advanced airway insertion. We used these 2 models because (1) the first model enabled us to report the estimate of effect size of advanced airway insertion, using at risk of receiving advanced airway insertion as the reference, at each categorized timing and (2) the second model enabled us to report the interaction between the advanced airway insertion and the timing of the airway insertion attempt.

We conducted 2 sensitivity analyses. In the first sensitivity analysis, we defined the main exposure as the interval between the first EMS arrival and the first laryngeal tube or endotracheal intubation attempt, regardless of the level of EMS response (ie, basic life support or advanced life support). We used the same exclusion criteria as in the primary analysis except that we excluded patients with unknown time of the first EMS arrival. We carried out similar time-dependent propensity score and risk-set

matching analyses. We used the same covariates as in the primary analysis except that we used shock delivery after EMS arrival as a time-dependent covariate in this sensitivity analysis.

In the second sensitivity analysis, we defined the main exposure as the interval between advanced life support arrival and successful laryngeal tube insertion or endotracheal intubation. The time of successful advanced airway insertion was defined as time of secured advanced airway after placement confirmation. We used the same exclusion criteria as in the primary analysis except that we excluded patients with unknown time of successful laryngeal tube or endotracheal intubation or negative value in the interval between advanced life support arrival and the successful laryngeal tube insertion or endotracheal intubation. All statistical analyses were performed with R software, version 3.5.1 (www.r-project.org, Vienna, Austria).

RESULTS

Characteristics of Study Subjects

Of 3,004 patients enrolled in the parent trial, we included 2,146 patients in our study (Figure 1). Of them, 1,091 patients (50.8%) were assigned to initial laryngeal tube and 1,055 (49.2%) were assigned to initial endotracheal intubation strategies. Patient characteristics are shown in Table 1. Among those randomized to an initial laryngeal tube strategy, 949 patients (87.0%) received initial attempts of laryngeal tube insertion, 41 (3.8%) received initial attempts of endotracheal intubation, and 101 (9.3%) received no advanced airway insertion attempt. Among those randomized to an initial endotracheal intubation strategy, 822 (77.9%) patients received initial attempts of endotracheal intubation, 93 (8.8%) received initial attempts of laryngeal tube, and 140 (13.3%) received no advanced airway insertion attempt. The median interval between advanced life support arrival and the first laryngeal tube attempt was 8 minutes (interquartile range [IQR] 6 to 11) in the cohort randomized to an initial laryngeal tube strategy, and the median interval between advanced life support arrival and the first endotracheal intubation attempt was 11 minutes (IQR 8 to 14) in the cohort randomized to an initial endotracheal intubation strategy.

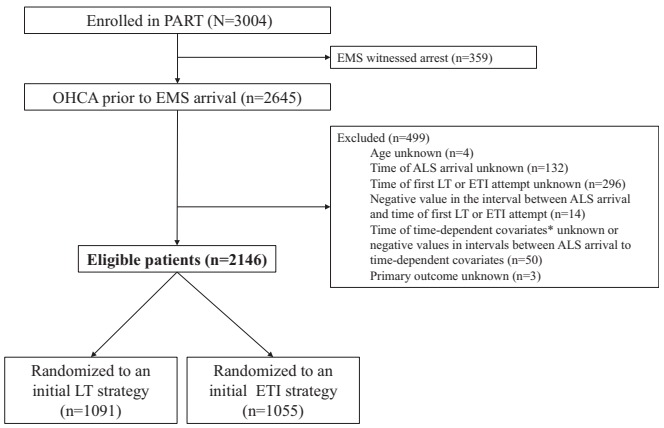


Figure 1. Patient flow. *ALS,*advanced life support; *EMS,* emergency medical services; *ETI,* endotracheal intubation; *LT,* laryngeal tube; *OHCA,* out-of-hospital cardiac arrest

Main Results

Of the 2,146 patients included in the study, 923 patients who received the first attempts of laryngeal tube insertion in the cohort randomized to an initial laryngeal tube strategy and 776 patients who received the first attempts of endotracheal intubation in the cohort randomized to an initial endotracheal intubation strategy were matched with at-risk patients (Table 2). Among those matched as at-risk patients in the laryngeal tube and endotracheal intubation cohorts, 746 (80.8%) and 598 (77.1%) received the first laryngeal tube and endotracheal intubation attempts, respectively, after the matching. In both matched cohorts, standardized differences were within 0.25 for all covariates, indicating good postmatching balance. In the matched cohort of an initial laryngeal tube strategy, the median interval between advanced life support arrival and the first laryngeal tube attempt was 8 minutes (IQR 6 to 11) in the laryngeal tube group and 12 minutes (IQR 9 to 14) in the at-risk of receiving laryngeal tube group (Table 2). In the matched cohort of initial endotracheal intubation strategy, the median interval between advanced life support arrival and the first endotracheal intubation attempt was 11 minutes (IQR 8 to 14) in the endotracheal intubation group and 15 minutes (IQR 12 to 18) in the at-risk of receiving endotracheal intubation group.

In the matched cohort of initial laryngeal tube, survival to hospital discharge (67/923 [7.3%] versus 60/923 [6.5%]; RR 1.32 [95% CI 0.90 to 1.92]), favorable neurologic status at hospital discharge (16/919 [1.7%] versus 20/921 [2.2%]; RR 1.04 [95% CI 0.51 to 2.12]), and 72-hour survival (138/923 [15.0%] versus 117/923 [12.7%]; RR 1.26 [95% CI 0.97 to 1.64]) did not differ between those who received the first laryngeal tube attempts and those who were at risk of receiving laryngeal tube attempts at the time of matching (Table 3). In the matched cohort of initial endotracheal intubation, survival to hospital discharge (37/776 [4.8%] versus 38/

Table 2. Patient characteristics in time-dependent propensity score-matched cohorts.

	Randomized to an Initial Laryngeal Tube Strategy			Randomized to an Initial Endotracheal Intubation Strategy		
Variable	**At risk of laryngeal tube insertion attempt (n=923)**	**Laryngeal tube insertion attempt (n=923)**	**Standardized difference**	**At risk of endotracheal intubation attempt (n=776)**	**Endotracheal intubation attempt (n=776)**	**Standardized difference**
Age, median (IQR), y	64 (52-76)	64 (53-76)	0.002	63.5 (51.75-75)	64.5 (53-76)	0.064
Male, n (%)	592 (64.1)	584 (63.3)	0.018	472 (60.8)	467 (60.2)	0.013
Race, n (%)			0.005			0.049
White	506 (54.8)	508 (55.0)		431 (55.5)	413 (53.2)	
Non-White	232 (25.1)	230 (24.9)		219 (28.2)	234 (30.2)	
Unknown	185 (20.0)	185 (20.0)		126 (16.2)	129 (16.6)	
First recorded rhythm, n (%)			0.079			0.053
Shockable	153 (16.6)	180 (19.5)		117 (15.1)	132 (17.0)	
Nonshockable	745 (80.7)	722 (78.2)		643 (82.9)	628 (80.9)	
Unknown	25 (2.7)	21 (2.3)		16 (2.1)	16 (2.1)	
Location, n (%)			0.091			0.096
Street/highway	20 (2.2)	18 (2.0)		18 (2.3)	25 (3.2)	
Public building	4 (0.4)	8 (0.9)		5 (0.6)	7 (0.9)	
Place of recreation	6 (0.7)	3 (0.3)		6 (0.8)	5 (0.6)	
Industrial place	2 (0.2)	2 (0.2)		4 (0.5)	3 (0.4)	
Home	653 (70.7)	675 (73.1)		528 (68.0)	537 (69.2)	
Health care facility	44 (4.8)	40 (4.3)		29 (3.7)	27 (3.5)	
Residential institution	133 (14.4)	119 (12.9)		123 (15.9)	114 (14.7)	
Other public property	56 (6.1)	53 (5.7)		59 (7.6)	54 (7.0)	
Other non-public property	1 (0.1)	1 (0.1)		4 (0.5)	3 (0.4)	
Unknown	4 (0.4)	4 (0.4)		0 (0.0)	1 (0.1)	
Witnessed collapse, n (%)			0.056			0.042
Bystander	308 (33.4)	332 (36.0)		288 (37.1)	290 (37.4)	
Unwitness	507 (54.9)	484 (52.4)		436 (56.2)	426 (54.9)	
Unknown	108 (11.7)	107 (11.6)		52 (6.7)	60 (7.7)	
Bystander CPR, n (%)	487 (52.8)	486 (52.7)	0.002	443 (57.1)	439 (56.6)	0.01
Bystander AED shock delivery, n (%)	21 (2.3)	20 (2.2)	0.007	17 (2.2)	20 (2.6)	0.025
EMS shock delivery before ALS arrival, n (%)	14 (1.5)	18 (2.0)	0.033	12 (1.5)	11 (1.4)	0.011
EMS response time (interval between 9-1-1 call and first EMS arrival), median (IQR), minutes	5 (4-6)	5 (4-6)	0.092	5 (4-6)	5 (4-7)	0.09
Shock delivery after ALS arrival before matching, n (%)	134 (14.5)	152 (16.5)	0.054	133 (17.1)	128 (16.5)	0.017
Epinephrine administration before matching, n (%)	497 (53.8)	449 (48.6)	0.104	586 (75.5)	562 (72.4)	0.071
Departure from the scene before matching, n (%)	19 (2.1)	7 (0.8)	0.11	10 (1.3)	13 (1.7)	0.032

Table 2. Continued.

Variable	Randomized to an Initial Laryngeal Tube Strategy			Randomized to an Initial Endotracheal Intubation Strategy		
	At risk of laryngeal tube insertion attempt (n=923)	Laryngeal tube insertion attempt (n=923)	Standardized difference	At risk of endotracheal intubation attempt (n=776)	Endotracheal intubation attempt (n=776)	Standardized difference
Randomization cluster			0.141			0.161
A	5 (0.5)	7 (0.8)		16 (2.1)	11 (1.4)	
B	4 (0.4)	4 (0.4)		0 (0.0)	2 (0.3)	
C	197 (21.3)	177 (19.2)		265 (34.1)	243 (31.3)	
D	25 (2.7)	25 (2.7)		25 (3.2)	25 (3.2)	
E	59 (6.4)	63 (6.8)		35 (4.5)	42 (5.4)	
F	99 (10.7)	87 (9.4)		49 (6.3)	53 (6.8)	
G	223 (24.2)	218 (23.6)		140 (18.0)	161 (20.7)	
H	97 (10.5)	105 (11.4)		88 (11.3)	74 (9.5)	
I	33 (3.6)	24 (2.6)		15 (1.9)	12 (1.5)	
J	20 (2.2)	15 (1.6)		15 (1.9)	21 (2.7)	
K	0 (0.0)	0 (0.0)		5 (0.6)	3 (0.4)	
L	133 (14.4)	158 (17.1)		89 (11.5)	87 (11.2)	
M	28 (3.0)	40 (4.3)		34 (4.4)	42 (5.4)	
Initial attempt of laryngeal tube insertion						
Yes, n (%)	746 (80.8)	923 (100.0)	N/A	70 (9.0)	0 (0.0)	N/A
Interval between advanced life support arrival and LT attempt, median (IQR), minutes	12 (9-14)	8 (6-11)	N/A	16 (13-20)	N/A	N/A
Initial attempt of endotracheal intubation						
Yes, n (%)	56 (6.1)	0 (0.0)	N/A	598 (77.1)	776 (100.0)	N/A
Interval between ALS arrival and endotracheal intubation attempt, median (IQR), minutes	16 (11-21)	N/A	N/A	15 (12-18)	11 (8-14)	N/A

N/A, not applicable.

776 [4.9%]; RR 1.03 [95% CI 0.62 to 1.71]), favorable neurologic status at hospital discharge (12/776 [1.5%] versus 22/776 [2.8%]; RR 0.67 [95% CI 0.29 to 1.55]), and 72-hour survival (85/776 [11.0%] versus 65/776 [8.4%]; RR 1.34 [95% CI 0.94 to 1.91]) did not differ between those who received the first endotracheal intubation attempts and those who were at risk of receiving endotracheal intubation attempts at the time of matching.

The estimated effect of the first laryngeal tube attempt by timing after advanced life support arrival is shown in Figure 2. Timing of laryngeal tube insertion attempt was not associated with survival to hospital discharge: 0 to lesser than 5 minutes (RR=1.35, 95% CI 0.53 to 3.44); 5 to lesser than 10 minutes (RR=1.07, 95% CI 0.66 to 1.73); 10 to lesser than 15 minutes (RR=1.17, 95% CI 0.60 to 2.31); or 15 to lesser than 20 minutes (RR=2.09, 95% CI 0.35 to 12.47) after advanced life support arrival (Figure 2A). Similarly, the estimated effect of the first laryngeal tube attempt on favorable neurologic status at hospital discharge (Figure 2B) and 72-hour survival (Figure 2C) were not significant across all categorized timing of the first laryngeal tube attempts. When timing of the first laryngeal tube attempts was treated as a continuous

Table 3. Outcomes in time-dependent propensity score-matched cohort.

	No (%) Patients with Outcome/Total Patients		
Outcome	**At risk of LT insertion attempt**	**LT insertion attempt**	**Risk Ratio (95% CI)**
Randomized to an initial LT strategy			
Survival to hospital discharge	60/923 (6.5%)	67/923 (7.3%)	1.32 (0.90-1.92)
Favorable neurologic outcome at hospital discharge	20/921 (2.2%)	16/919 (1.7%)	1.04 (0.51-2.12)
72-hour survival	117/923 (12.7%)	138/923 (15.0%)	1.26 (0.97-1.64)
	At risk of ETI attempt	ETI attempt	
Randomized to an initial ETI strategy			
Survival to hospital discharge	38/776 (4.9%)	37/776 (4.8%)	1.03 (0.62-1.71)
Favorable neurologic outcome at hospital discharge	22/776 (2.8%)	12/776 (1.5%)	0.67 (0.29-1.55)
72-hour survival	65/776 (8.4%)	85/776 (11.0%)	1.34 (0.94-1.91)

No, number.

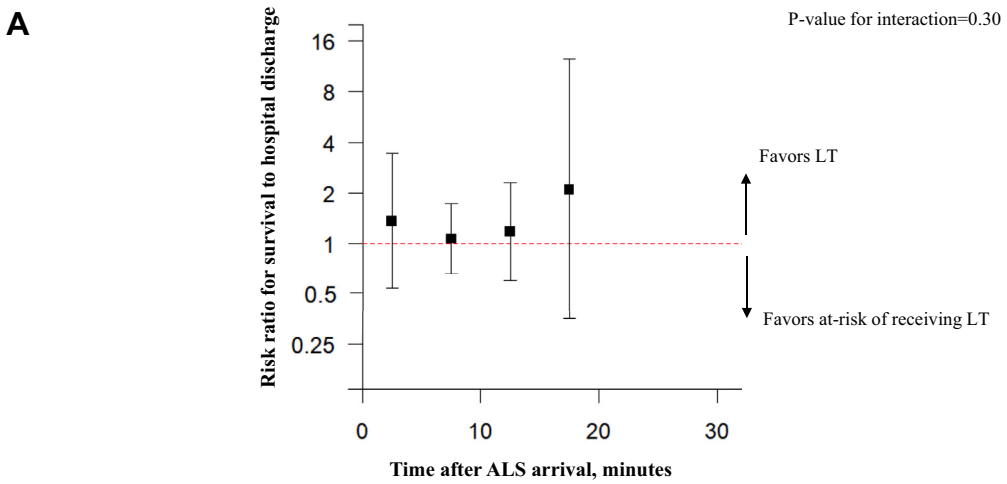
variable, the interaction between the first laryngeal tube attempt and time to matching after advanced life support arrival was not significant for each outcome (Figure 2).

The estimated effect of the first endotracheal intubation attempt by timing after advanced life support arrival is shown in Figure 3. Timing of endotracheal intubation attempt was not associated with survival: 0 to lesser than 5 minutes (RR=0.50, 95% CI 0.05 to 4.87); 5 to lesser than 10 minutes (RR=1.20, 95% CI 0.51 to 2.81); 10 to lesser than 15 minutes (RR=1.03, 95% CI 0.49 to 2.14); 15 to lesser than 20 minutes (RR=0.85, 95% CI 0.30 to 2.42); or more than/equal to 20 minutes (RR=0.71, 95% CI 0.07 to 7.14) (Figure 3A). Similarly, the estimated effect of the first endotracheal intubation attempt on favorable neurologic status at hospital discharge (Figure 3B) and 72-hour survival (Figure 3C) were also not significant across all categorized timing of the first endotracheal intubation attempts. We observed no significant interaction between the first endotracheal intubation attempt and time to matching for each outcome (Figure 3).

In the sensitivity analyses, we present patient flow (Figures E2 and E5, available at http://www.annemergmed.com), baseline patient characteristics (Tables E1 and E4, available at http://www.annemergmed.com), and characteristics of time-dependent propensity score-matched cohorts (Tables E2 and E5, available at http://www.annemergmed.com). The matched cohorts had good postmatching balance with standardized differences for all covariates within 0.25 (Tables E2 and E5, available at http://www.annemergmed.com). Treatment effects of timing of the first laryngeal tube and endotracheal intubation attempts on each outcome were not significant and similar to the results in the primary analysis (Table E3, available at http://www.annemergmed.com). Treatment effects of timing of the successful laryngeal tube insertion and endotracheal intubation on each outcome were not significant and were similar to the results in the primary analysis except that timing of the successful laryngeal tube insertion was associated with 72-hour survival (Table E6, available at http://www.annemergmed.com). The estimated effects of the first laryngeal tube and endotracheal intubation attempts (Figures E3 and E4, available at http://www.annemergmed.com) by timing after the first EMS arrival and the successful laryngeal tube insertion and endotracheal intubation (Figures E6 and E7, available at http://www.annemergmed.com) by timing after advanced life support arrival are shown. In both matched cohorts of initial laryngeal tube and endotracheal intubation strategies in the 2 sensitivity analyses, we observed that the interactions between advanced airway insertion and time to matching were not significant.

LIMITATIONS

First, accurate measurement of time variables in the out-of-hospital setting is challenging, and precision of the collected time variables is one limitation. However, the PART collected time variables using standardized definitions and reporting practices as described in the methods section. Usage of a clinical trial with such data collecting systems was intended to minimize this limitation. Second, some of the models estimating effect size of laryngeal tube and endotracheal intubation attempts did not converge because of lack of outcome events, suggesting that we had a limited sample size, despite use of a large clinical trial dataset. Third, time to advanced airway insertion attempt and time to successful advanced airway insertion may reflect resuscitation practices of individual



Time after ALS arrival, minutes	0 to <5	5 to <10	10 to <15	15 to <20	≥20
LT insertion attempt	9/71 (12.7%)	32/413 (7.7%)	21/338 (6.2%)	3/86 (3.5%)	2/15 (13.3%)
At-risk of receiving LT insertion attempt	7/71 (9.9%)	31/413 (7.5%)	20/338 (5.9%)	2/86 (2.3%)	0/15 (0%)
Risk ratio (95% CI)	1.35 (0.53-3.44)	1.07 (0.66-1.73)	1.17 (0.60-2.31)	2.09 (0.35-12.47)	*

Figure 2. Association between timing of the first LT insertion attempt after ALS arrival and *A*, survival to hospital discharge; *B*, favorable neurologic status at hospital discharge; and *C*, 72-hour survival for patients who were randomized to an initial LT strategy. Box plots indicate point estimates of treatment effects of LT insertion with 95% CIs, treating timing as a categorical variable. Box plots were placed at median time for each categorized time. *P* values for interactions between the first LT insertion attempt and time to matching were reported. *The model did not converge.

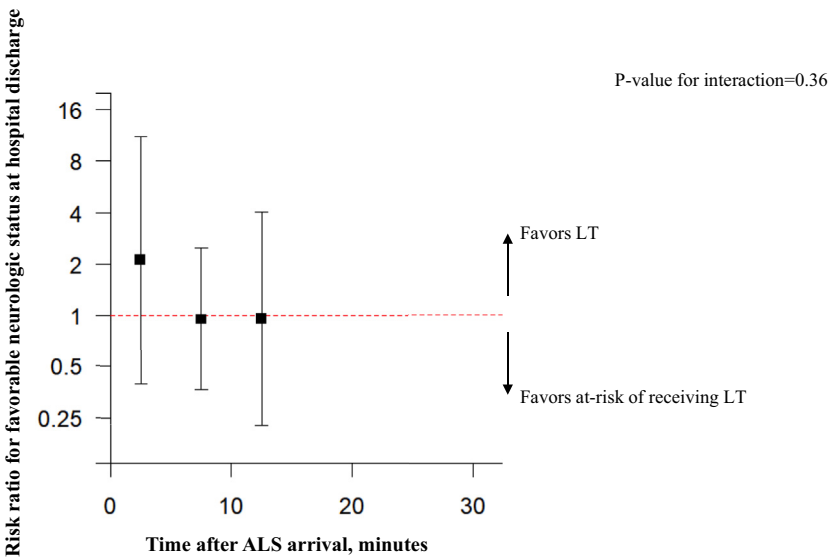
EMS systems since the EMS clinicians in the pragmatic trial followed existing local protocols for out-of-hospital cardiac arrest care.[10] We included the randomization cluster in the time-dependent propensity score model and accounted for the clustering of patients. However, residual clustering effects are possible. Fourth, we cannot fully eliminate confounding by indication.[27] The specific clinical scenario for each patient may have affected the decision regarding timing of advanced airway management. Lastly, the findings may not be externally valid at other EMS systems because the PART included EMS agencies based on their interest in and ability to conduct an out-of-hospital clinical trial.

DISCUSSION

In this secondary analysis of a cluster randomized controlled trial comparing the effectiveness of strategies of initial laryngeal tube insertion versus initial endotracheal intubation for adult patients with out-of-hospital cardiac arrest, we found that timing of the first laryngeal tube insertion and endotracheal intubation after advanced life support arrival was not associated with survival to hospital discharge, favorable neurologic outcome at hospital discharge, or 72-hour survival. The findings were consistent in sensitivity analyses, investigating timing of the initial intraarrest laryngeal tube insertion and endotracheal intubation attempts after the first EMS unit arrival and successful laryngeal tube insertion and endotracheal intubation after advanced life support arrival, except timing of successful laryngeal tube insertion was associated with 72-hour survival.

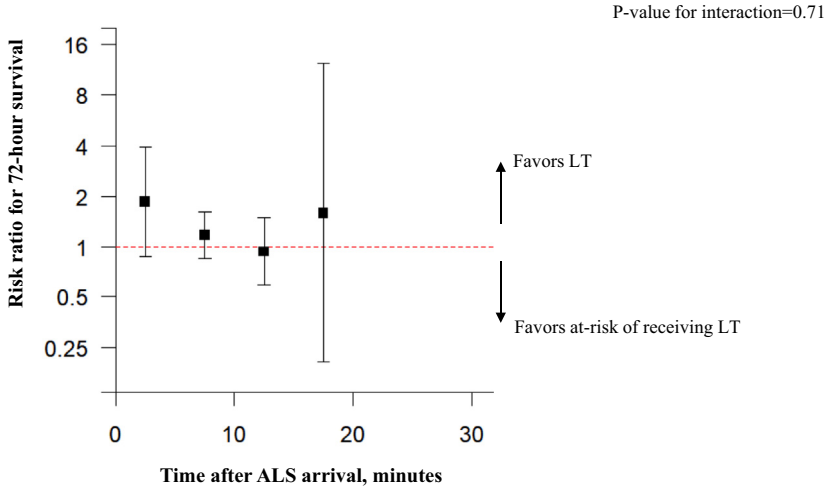
Multiple prior studies showed associations between timing of advanced airway management and favorable patient outcomes. An observational study in Osaka, Japan including over 27,400 adult patients with out-of-hospital cardiac arrest showed that early advanced airway management (less than 5 minutes after cardiopulmonary resuscitation [CPR] by EMS clinicians) was associated with improved 1-month survival (adjusted odds ratio [OR] 1.42 [95% CI 1.23 to 1.65]) and favorable neurologic status at 1 month, defined as Cerebral Performance Category (CPC) scale 1 or 2 (adjusted OR 1.58 [95% CI 1.24 to 2.02]), compared with late

B



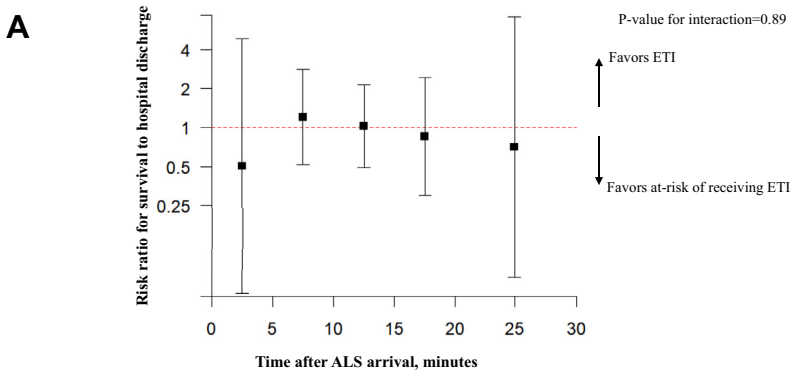
Time after ALS arrival, minutes	0 to <5	5 to <10	10 to <15	15 to <20	≥20
LT insertion attempt	4/71 (5.6%)	9/410 (2.2%)	3/337 (0.9%)	0/86 (0%)	0/15 (0%)
At-risk of receiving LT insertion attempt	2/71 (2.8%)	11/411 (2.7%)	6/338 (1.8%)	1/86 (1.2%)	0/15 (0%)
Risk ratio (95% CI)	2.11 (0.40-11.15)	0.95 (0.36-2.48)	0.95 (0.23-4.05)	*	*

C

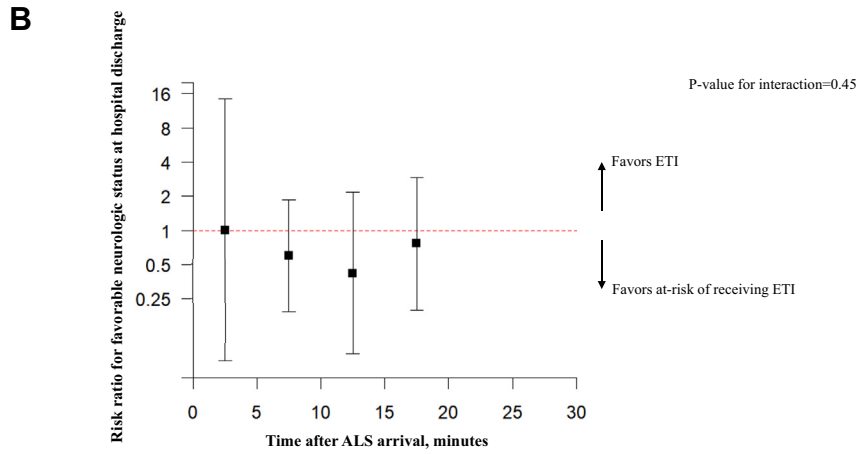


Time after ALS arrival, minutes	0 to <5	5 to <10	10 to <15	15 to <20	≥20
LT insertion attempt	16/71 (22.5%)	69/413 (16.7%)	39/338 (11.5%)	11/86 (12.8%)	3/15 (20.0%)
At-risk of receiving LT insertion attempt	9/71 (12.7%)	61/413 (14.8%)	40/338 (11.8%)	7/86 (8.1%)	0/15 (0%)
Risk ratio (95% CI)	1.87 (0.88-3.95)	1.18 (0.85-1.63)	0.94 (0.59-1.50)	1.58 (0.20-12.28)	*

Figure 2. Continued.



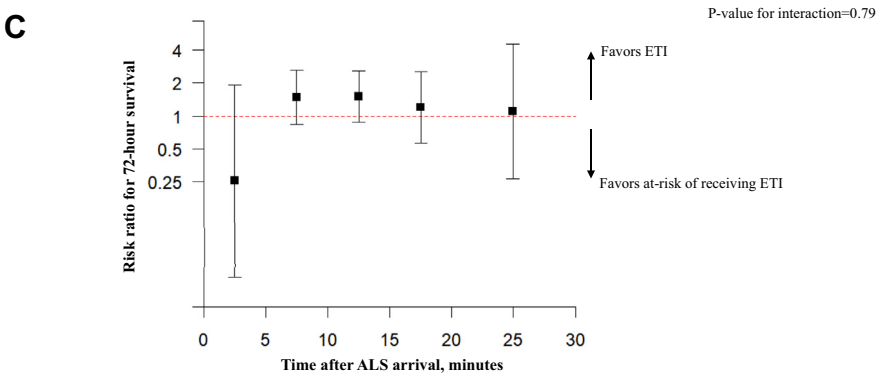
Time after ALS arrival, minutes	0 to <5	5 to <10	10 to <15	15 to <20	≥20
ETI attempt	1/24 (4.2%)	12/218 (5.5%)	16/313 (5.1%)	7/168 (4.2%)	1/53 (1.9%)
At-risk of receiving ETI attempt	2/24 (8.3%)	10/218 (4.6%)	15/313 (4.8%)	9/168 (5.4%)	2/53 (3.8%)
Risk ratio (95% CI)	0.50 (0.05-4.87)	1.20 (0.51-2.81)	1.03 (0.49-2.14)	0.85 (0.30-2.42)	0.71 (0.07-7.14)



Time after ALS arrival, minutes	0 to <5	5 to <10	10 to <15	15 to <20	≥20
ETI attempt	1/24 (4.2%)	5/218 (2.3%)	2/313 (0.6%)	4/168 (2.4%)	0/53 (0%)
At-risk of receiving ETI attempt	1/24 (4.2%)	8/218 (3.7%)	7/313 (2.2%)	6/168 (3.6%)	0/53 (0%)
Risk ratio (95% CI)	1.00 (0.07-14.35)	0.60 (0.19-1.86)	0.42 (0.08-2.17)	0.76 (0.20-2.93)	*

Figure 3. Association between timing of the first endotracheal intubation attempt after ALS arrival and *A*, survival to hospital discharge; *B*, favorable neurologic status at hospital discharge; and *C*, 72-hour survival for patients who were randomized to an initial endotracheal intubation strategy. Box plots indicate point estimates of treatment effects of endotracheal intubation with 95% CIs, treating timing as a categorical variable. Box plots were placed at median time for each categorized time. *P* values for interactions between the first ETI attempt and time to matching were reported. *The model did not converge. *ALS,* advanced life support; *ETI,* endotracheal intubation.

advanced airway management (more than/equal to 5 minutes after CPR by EMS clinicians).[28] The study also reported that each minute of delay to advanced airway management after initiation of CPR by EMS clinicians was associated with decreased chances of 1-month survival (adjusted OR 0.93 [95% CI 0.91 to 0.95]) and favorable neurologic outcome at 1 month (adjusted OR 0.90 [95% CI 0.87 to 0.94]). Another observational



Time after ALS arrival, minutes	0 to <5	5 to <10	10 to <15	15 to <20	≥20
ETI attempt	1/24 (4.2%)	28/218 (12.8%)	36/313 (11.5%)	16/168 (9.5%)	4/53 (7.5%)
At-risk of receiving ETI attempt	4/24 (16.7%)	20/218 (9.2%)	23/313 (7.3%)	14/168 (8.3%)	4/53 (7.5%)
Risk ratio (95% CI)	0.26 (0.03-1.93)	1.49 (0.84-2.64)	1.50 (0.87-2.57)	1.20 (0.56-2.56)	1.10 (0.27-4.50)

Figure 3. Continued.

study in Osaka including over 5,300 adults with bystander-witnessed out-of-hospital cardiac arrest demonstrated that each minute of delay to advanced airway management after bystander-witnessed collapse was associated with decreased chance of CPC scale 1 or 2 at 1 month (adjusted OR 0.91 [95% CI 0.88 to 0.95]).[29] A cohort study in King County in Washington, USA including 693 patients with bystander-witnessed out-of-hospital cardiac arrest between 1991 and 2003 demonstrated that early endotracheal intubation (more than/equal to 12 minutes after bystander-witnessed collapse) was associated with an increased chance of survival to hospital discharge (adjusted OR 2.38 [95% CI 1.45 to 3.85]) compared with late endotracheal intubation (more than/equal to 13 minutes after bystander-witnessed collapse).[30] A secondary analysis of the Resuscitation Outcomes Consortium Prehospital Resuscitation using an Impedance Valve and Early versus Delayed trial including over 7,500 instances of bystander-witnessed out-of-hospital cardiac arrest between 2007 and 2010 at 10 sites in the United States and Canada also reported that each additional minute from EMS arrival to successful advanced airway placement was associated with decreased survival to hospital discharge for shockable (adjusted OR 0.91 [95% CI 0.89 to 0.93]) and nonshockable rhythms (adjusted OR 0.89 [95% CI 0.85 to 0.92]).[31]

Although these previous studies reported that early advanced airway management was associated with improved patient outcomes, resuscitation time bias or other factors may have affected these findings.[11] Since patients with later advanced airway management tend to have longer resuscitation duration than those with earlier advanced airway management, resuscitation time bias skews the timing effect of advanced airway management toward favoring earlier advanced airway management, and it is therefore important to control for this bias.[11] Using time-dependent propensity score and risk-set matching analyses, we accounted for potential resuscitation time bias, and, therefore, our results are believed to be less biased than those of these prior studies.

Our use of a clinical trial dataset enabled us to stratify the patient population into assigned initial laryngeal tube and endotracheal intubation strategies and explore the timing effect of the initial airway strategies. In the propensity score matched cohorts, 80.8% of at-risk patients in the cohort of initial laryngeal tube strategy and 77.1% of at-risk patients in the cohort of initial endotracheal intubation strategy subsequently received laryngeal tube and endotracheal intubation attempts, respectively. Since the majority of patients in each cohort received the assigned initial airway strategy, we were able to compare the treatment effects of laryngeal tube and endotracheal intubation attempts across timing of each advanced airway insertion attempt.

Our RRs should be interpreted as the ratio of the risk of outcomes with advanced airway insertion attempt at any given minute compared to the risk of outcomes without

advanced airway insertion attempt at the same minute. This interpretation addresses the question, "Should this patient receive an advanced airway insertion attempt now compared to not receiving an advanced airway insertion attempt now?" and is clinically relevant as a provider is unaware at that point whether the patient will receive advanced airway insertion or not in the future. In the primary analysis, we chose timing of the first advanced airway insertion attempt, not timing of successful advanced airway insertion, because timing of the first advanced airway insertion attempt is an easily modifiable factor since EMS clinicians can decide when they initiate advanced airway insertion attempts. The timing of successful advanced airway insertion is less modifiable as it is confounded by patient factors (eg, presence of a difficult airway) and provider factors (eg, training and experience). As one of our sensitivity analyses, we evaluated the timing of successful advanced airway insertion. The findings showed nonsignificant interactions between the successful laryngeal tube insertion or endotracheal intubation and time to matching, similar to the results of the primary analysis, suggesting that timing of advanced airway insertion was not associated with patient outcome, regardless of the timing of attempt or successful placement.

Our results did not identify a single time point that was associated with improved patient outcomes. These findings suggest that the optimal timing of advanced airway management depends on the clinical scenario of each patient and highlight the importance of clinical judgment of EMS clinicians in terms of when to initiate advanced airway insertion attempts. Further, it is unclear whether treatment modification of timing of the initial advanced airway insertion attempt exists (ie, some phenotypes of patients may benefit from early or late advanced airway management), and this research question needs further investigation.

In summary, in this secondary analysis of a clinical trial dataset, we found that timing of advanced airway insertion attempt after advanced life support arrival was not significantly associated with survival to hospital discharge, favorable neurologic outcome at hospital discharge, or 72-hour survival after out-of-hospital cardiac arrest.

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Author contributions: MO, SK, and JI conceived and designed the study. TPA, JLB, JNC, MRD, MH, AHI, NL, JRL, GN, RS, HEW, and CWC supervised the conduct of the study. SK analyzed the data. MO drafted the manuscript, and all authors contributed substantially to its revision. MO takes responsibility for the paper as a whole.

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