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ORIGINAL RESEARCH

Timing of Prehospital Advanced Airway Management for Adult Patients With Out-of-Hospital Cardiac Arrest: A Nationwide Cohort Study in Japan

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BACKGROUND: The timing of advanced airway management (AAM) on patient outcomes after out-of-hospital cardiac arrest has not been fully investigated. We evaluated the association between the timing of prehospital AAM and 1-month survival.

METHODS AND RESULTS: We conducted a secondary analysis of a prospective, nationwide, population-based out-of-hospital cardiac arrest registry in Japan. We included emergency medical services–treated adult (≥18 years) out-of-hospital cardiac arrests from 2014 through 2017, stratified into initial shockable or nonshockable rhythms. Patients who received AAM at any minute after emergency medical services–initiated cardiopulmonary resuscitation underwent risk-set matching with patients who were at risk of receiving AAM within the same minute using time-dependent propensity scores. Eleven thousand three hundred six patients with AAM in shockable and 163 796 with AAM in nonshockable cohorts, respectively, underwent risk-set matching. For shockable rhythms, the risk ratios (95% CIs) of AAM on 1-month survival were 1.01 (0.89–1.15) between 0 and 5 minutes, 1.06 (0.98–1.15) between 5 and 10 minutes, 0.99 (0.87–1.12) between 10 and 15 minutes, 0.74 (0.59–0.92) between 15 and 20 minutes, 0.61 (0.37–1.00) between 20 and 25 minutes, and 0.73 (0.26–2.07) between 25 and 30 minutes after emergency medical services–initiated cardiopulmonary resuscitation. For nonshockable rhythms, the risk ratios of AAM were 1.12 (1.00–1.27) between 0 and 5 minutes, 1.34 (1.25–1.44) between 5 and 10 minutes, 1.39 (1.26–1.54) between 10 and 15 minutes, 1.20 (0.99–1.45) between 15 and 20 minutes, 1.18 (0.80–1.73) between 20 and 25 minutes, 0.63 (0.29–1.38) between 25 and 30 minutes, and 0.44 (0.11–1.69) after 30 minutes.

CONCLUSIONS: In this observational study, the timing of AAM was not statistically associated with improved 1-month survival for shockable rhythms, but AAM within 15 minutes after emergency medical services–initiated cardiopulmonary resuscitation was associated with improved 1-month survival for nonshockable rhythms.

Key Words: advanced airway management ■ emergency medical services ■ out-of-hospital cardiac arrest

Out-of-hospital cardiac arrest (OHCA) is a major public health problem, annually affecting >356 000 people in the United States and 127 000 in Japan with high mortality rate.[1,2] The 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care recommend considering advanced airway management (AAM) (ie, supraglottic airway [SGA] placement or endotracheal intubation [ETI] after 2 attempts of shock delivery for shockable rhythms and after the initial 2 minutes of CPR for nonshockable rhythms).[3] However, evidence about the optimal timing of each

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CLINICAL PERSPECTIVE

What Is New?

- In a secondary analysis of the prospective, nationwide, population-based out-of-hospital cardiac arrest registry in Japan using time-dependent propensity score and risk-set matching analyses, we did not detect an optimal timing of advanced airway management during resuscitation that was associated with improved 1-month survival for adult patients with shockable rhythms, but found that advanced airway management within 15 minutes after the initiation of cardiopulmonary resuscitation by emergency medical services providers was associated with improved 1-month survival for patients with nonshockable rhythms.

What Are the Clinical Implications?

- Advanced airway management within 15 minutes after the initiation of cardiopulmonary resuscitation by emergency medical services providers may be beneficial for adults with nonshockable rhythms.

Nonstandard Abbreviations and Acronyms

AAM	advanced airway management
CPC	Cerebral Performance Category
ETI	endotracheal intubation
OHCA	out-of-hospital cardiac arrest
ROSC	return of spontaneous circulation
SGA	supraglottic airway

AAM method is limited. The International Liaison Committee on Resuscitation Advanced Life Support Task Force evaluated the existing evidence about AAM during cardiac arrest in a 2019 systematic review.[4] The International Liaison Committee on Resuscitation was unable to draw conclusions about the ideal timing of AAM because of the critical risk of bias in all included studies.[4] The 2019 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations identified the optimal time point during CPR to change to different airway techniques (eg, from bag-mask ventilation to AAM) as one of the knowledge gaps, highlighting the importance of further investigation of the timing effect of AAM.[5]

Resuscitation time bias is an important limitation in prior studies comparing early AAM versus late AAM.[6] Because patients who achieved return of spontaneous circulation (ROSC) before any intra-arrest AAM are excluded from the cohort, patients with late AAM have longer mean resuscitation duration, and the effect of late AAM versus early AAM, therefore, appears to be biased toward a harmful effect.[6] One method to address resuscitation time bias when evaluating intra-arrest interventions is time-dependent propensity score and risk-set matching analyses.[6–10] However, no prior studies evaluated the timing of AAM for patients with OHCA using this methodology.

Our objective was to evaluate the association between the timing of prehospital AAM (ie, SGA placement or ETI during CPR and patient outcomes after OHCA using time-dependent propensity score and risk-set matching analyses).

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Setting

We conducted a secondary analysis of the All-Japan Utstein Registry, a prospective, nationwide, population-based OHCA registry.[9,10] All-Japan Utstein Registry prospectively collected emergency medical services (EMS)–assessed OHCA, using the Utstein Resuscitation Registry Template for OHCA.[9–14] Cardiac arrest was defined as lack of cardiac mechanical activity confirmed by lack of clinical evidence of a circulation.[11,12,14] In Japan, municipal governments provide EMS systems through local fire departments, and each ambulance crew consists of 3 EMS providers including at least 1 emergency life-saving technician who completed extensive training in prehospital care. All emergency life-saving technicians are permitted to insert SGA (eg, laryngeal tube and laryngeal mask) for patients with OHCA under online medical direction.[9,10] Since 2004, specially trained and certified emergency life-saving technicians have been permitted to perform ETI for patients with OHCA under online medical direction after completing additional training as described in the eMethods (Supporting information).[9,10] Additional details of the study setting are also provided in Data S1. The institutional review board of Osaka University Graduate School of Medicine approved this study and waived the need for informed consent because of de-identified data.

Study Participants

We screened the data of all patients with OHCA in the All-Japan Utstein Registry from January 2014 through December 2017, the most recent data available at the time of the analysis. The inclusion criteria of this study were age of 18 years or older, cardiac arrest before EMS arrival, cardiac arrest for which EMS providers attempted resuscitation, and cardiac arrest attended by an emergency life-saving technician. We defined attempted resuscitation as external shock delivery and/or chest compression by EMS providers.[11,12,14]

We excluded those (1) with age outliers (≥120 years); (2) with unknown initial rhythms; (3) with inappropriate resuscitation interval variables; (4) with unknown time-dependent or time-independent covariates described below; or (5) with an interval between emergency call to initiation of EMS CPR ≥30 minutes.[9] The resuscitation interval variables included an interval between initiation of CPR by EMS providers and successful placement of advanced airway device (interval between EMS CPR and AAM) (only for those who received AAM), an interval between initiation of EMS CPR and first shock delivery by EMS providers (only for those with shockable rhythms), an interval between initiation of EMS CPR and epinephrine administration by EMS providers (only for those who received epinephrine), an interval between initiation of EMS CPR and prehospital ROSC (only for those who had prehospital ROSC), an interval between emergency call and initiation of EMS CPR (EMS response time), and an interval between initiation of EMS CPR and hospital arrival. We defined OHCA with inappropriate resuscitation interval variables as any cases with negative values for the resuscitation intervals described above.

Exposure

The main exposure was the interval between the initiation of EMS CPR and the successful prehospital advanced airway device placement during CPR. The interval was defined in whole minutes (ie, AAM at 0 minute indicates that a patient received successful SGA placement or ETI within the same whole minute when EMS providers initiated CPR).

Outcomes

The primary outcome was 1-month survival. Secondary outcome was 1-month survival with favorable functional status, defined as a Cerebral Performance Category (CPC) scale of 1 or 2.[11,12,14] The functional outcome was determined by physicians who were responsible for the care of the patients at 1 month after successful resuscitation using the CPC scale. CPC 1 represents good cerebral performance; CPC 2, moderate cerebral disability; CPC 3, severe cerebral disability; CPC 4, coma or vegetative state; and CPC 5, death or brain death.[14] To collect the survival and functional outcomes, EMS providers in charge followed up all survivors and had interviews with the physicians at 1 month after the arrest.[9,15]

Statistical Analysis

We stratified the patients into 2 cohorts based on their initial rhythms on EMS arrival: shockable (ventricular defibrillation or pulseless ventricular tachycardia) or nonshockable (pulseless electrical activity or asystole) rhythms because current resuscitation guidelines recommend 2 algorithms according to the initial rhythms.[3] We present continuous variables as medians with interquartile ranges (IQR) and categorical variables as counts with proportions. We report standardized differences to describe differences in baseline patient characteristics.

To evaluate the association between the timing of AAM and outcomes, we performed time-dependent propensity score and risk-set matching analyses in each cohort of the initial rhythms.[7–10,16,17] We calculated propensity score as the estimated risk of receiving AAM after the initiation of EMS CPR using survival analysis with a Fine-Gray regression model with time-dependent covariates, time-independent covariates, a competing risk event, and a censoring event.[9,10,18] We therefore estimated time-varying probability of receiving AAM at each minute of CPR for each patient in each cohort of shockable and nonshockable rhythms. In the models, the dependent variable was the successful advanced airway device placement, and the initiation of EMS CPR was the time 0 because patients were at risk of receiving AAM only after this time point.

We present time-dependent and time-independent covariates in Table 1. The time-dependent covariates were shock delivery and epinephrine administration after the initiation of EMS CPR. The time-independent covariates were patient age, sex, year, season, day, time, prefecture categories (quartiles) based on the proportions of patients who received AAM among 47 prefectures, cause, witness status, initial rhythms (only in nonshockable cohort: pulseless electrical activity or asystole), layperson CPR, layperson automated external defibrillator shock delivery, dispatcher CPR instruction, prehospital physician involvement, and EMS response time. We used spline functions (B-spline) for continuous variables (age and EMS response time). Prefectures are the jurisdictional and administrative geographical division levels in Japan, and we included the prefecture categories to account for regional variation in outcomes.[13] The cause of arrest was presumed to be medical in origin unless the cause was trauma, drug overdose, drowning, electrocution, or asphyxia, based on the Utstein template.[14] We chose these covariates based on their association with survival from prior knowledge, biologic plausibility, and adequate ascertainment.[3,9,19] We included prehospital ROSC

Table 1. Characteristics of Adult Patients With Out-of-Hospital Cardiac Arrest With and Without AAM During CPR

Characteristics	Shockable rhythms			Nonshockable rhythms		
	No AAM (n=16 567)	AAM (n=11 390)	Standardized differences	No AAM (n=232 263)	AAM (n=164 040)	Standardized differences
Patient demographics						
Age, median (IQR), y	68 (56–78)	69 (59–79)	0.077	80 (69–87)	80 (70–87)	0.033
Sex, n (%)			0.028			0.053
Male	12 790 (77.2)	8925 (78.4)		125 290 (53.9)	92 785 (56.6)	
Arrest characteristics						
Year of arrest, n (%)			0.028			0.015
2014	4083 (24.6)	2930 (25.7)		57 100 (24.6)	41 084 (25.0)	
2015	4063 (24.5)	2746 (24.1)		57 016 (24.5)	40 727 (24.8)	
2016	4204 (25.4)	2801 (24.6)		57 699 (24.8)	40 193 (24.5)	
2017	4217 (25.5)	2913 (25.6)		60 448 (26.0)	42 036 (25.6)	
Season of arrest, n (%)			0.023			0.033
Spring	3992 (24.1)	2740 (24.1)		57 673 (24.8)	40 438 (24.7)	
Summer	3776 (22.8)	2530 (22.2)		45 143 (19.4)	30 259 (18.4)	
Fall	3939 (23.8)	2669 (23.4)		53 261 (22.9)	37 280 (22.7)	
Winter	4860 (29.3)	3451 (30.3)		76 186 (32.8)	56 063 (34.2)	
Day of arrest, n (%)			0.009			0.004
Weekday (Monday–Friday)	14 219 (85.8)	9738 (85.5)		199 834 (86.0)	141 386 (86.2)	
Weekend (Saturday and Sunday)	2348 (14.2)	1652 (14.5)		32 429 (14.0)	22 654 (13.8)	
Time of arrest, n (%)			0.004			0.005
Daytime (9:00–16:59)	5593 (33.8)	3822 (33.6)		78 070 (33.6)	55 522 (33.8)	
Nighttime (17:00–8:59)	10 974 (66.2)	7568 (66.4)		154 193 (66.4)	108 518 (66.2)	
Quartiles of prefecture preference for performing AAM			0.679			0.700
Quartile 1 (shockable: <24.2%; nonshockable: <26.6%), n (%)	4808 (29.0)	1194 (10.5)		80 089 (34.5)	18 519 (11.3)	
Quartile 2 (shockable: 24.4%–35.2%) (nonshockable: 26.6%–38.9%)	3738 (22.6)	1463 (12.8)		43 672 (18.8)	21 171 (12.9)	
Quartile 3 (shockable: 35.2%–48.3%) (nonshockable: 38.9%–53.2%)	4024 (24.3)	2999 (26.3)		57 355 (24.7)	48 625 (29.6)	
Quartile 4 (shockable: >48.3%) (nonshockable: >53.2%)	3997 (24.1)	5734 (50.3)		51 147 (22.0)	75 725 (46.2)	
Cause, n (%)			0.025			0.113
Medical	16 134 (97.4)	11 136 (97.8)		200 270 (86.2)	147 447 (89.9)	
Nonmedical	433 (2.6)	254 (2.2)		31 993 (13.8)	16 593 (10.1)	
Witness status, n (%)			0.167			0.120
Unwitnessed	4611 (27.8)	3578 (31.4)		159 011 (68.5)	105 930 (64.6)	
By family	6611 (39.9)	4974 (43.7)		41 746 (18.0)	36 648 (22.3)	

(*Continued*)

Table 1. Continued

Characteristics	Shockable rhythms			Nonshockable rhythms		
	No AAM (n=16 567)	AAM (n=11 390)	Standardized differences	No AAM (n=232 263)	AAM (n=164 040)	Standardized differences
By friend	1002 (6.0)	605 (5.3)		2275 (1.0)	2084 (1.3)	
By colleague	1266 (7.6)	657 (5.8)		1689 (0.7)	1239 (0.8)	
By passerby	1000 (6.0)	502 (4.4)		3949 (1.7)	1941 (1.2)	
By others	2077 (12.5)	1074 (9.4)		23 593 (10.2)	16 198 (9.9)	
Initial rhythms, n (%)			N/A			0.067
PEA	N/A	N/A		49 064 (21.1)	39 224 (23.9)	
Asystole	N/A	N/A		183 199 (78.9)	124 816 (76.1)	
Layperson interventions						
Layperson CPR, n (%)			0.066			0.093
Chest compression only CPR	8446 (51.0)	5633 (49.5)		101 274 (43.6)	78 585 (47.9)	
Chest compression with ventilation	1272 (7.7)	734 (6.4)		13 508 (5.8)	10 011 (6.1)	
No layperson CPR	6849 (41.3)	5023 (44.1)		117 481 (50.6)	75 444 (46.0)	
Public access AED shock delivery, n (%)	1020 (6.2)	471 (4.1)	0.092	2075 (0.9)	1435 (0.9)	0.002
EMS interventions						
Dispatcher CPR instruction, n (%)	8987 (54.2)	6699 (58.8)	0.092	133 726 (57.6)	104 859 (63.9)	0.130
Prehospital physician involvement, n (%)	1002 (6.0)	624 (5.5)	0.024	7539 (3.2)	4056 (2.5)	0.046
Interval between emergency call and initiation of EMS CPR, median (IQR), min	8 (7–10)	9 (7–11)	0.126	9 (7–11)	9 (7–11)	0.035
EMS shock delivery, n (%)	15 760 (95.1)	11 023 (96.8)	0.084	6505 (2.8)	7098 (4.3)	0.082
Interval between initiation of EMS CPR and EMS shock delivery, median (IQR), min	1 (1–2)	1 (1–2)	0.015	9 (5–15)	12 (6–20)	0.317
Epinephrine administration, n (%)	3645 (22.0)	5483 (48.1)	0.570	23 829 (10.3)	49 947 (30.4)	0.518
Interval between initiation of EMS CPR and epinephrine administration, median (IQR), min	13 (9–17)	13 (9–18)	0.049	14 (10–18)	14 (10–19)	0.073
Type of AAM			N/A			N/A
SGA	N/A	9753 (85.6)		N/A	131 204 (80.0)	
Laryngeal tube	N/A	9000 (79.0)		N/A	121 952 (74.3)	
Laryngeal mask	N/A	753 (6.6)		N/A	9252 (5.6)	
ETI	N/A	1637 (14.4)		N/A	32 836 (20.0)	
Interval between initiation of EMS CPR and AAM, median (IQR), min	N/A	8 (5–12)	N/A	N/A	8 (5–12)	N/A

AAM indicates advanced airway management; AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ETI, endotracheal intubation; IQR, interquartile range; N/A, not applicable; PEA, pulseless electrical activity; and SGA supraglottic airway.

before AAM as a competing risk event in the model because (1) intra-arrest AAM never occurs after ROSC except in cases with re-arrest after ROSC, (2) our interest was the timing of AAM for initial arrest, and (3) ROSC is an informative censoring event. We modeled hospital arrival as a censoring event because our main interest was the timing of AAM in the prehospital setting.

In each cohort of the initial rhythms, using the calculated time-dependent propensity scores, each patient who received AAM at any given minute after the initiation of EMS CPR was sequentially matched with a patient who was at risk of receiving AAM and had the nearest propensity score within the same minute in a 1-to-1 fashion (risk-set matching). At-risk patients, therefore, included those who received AAM after the matching and those who did not receive AAM 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 or as patients receiving AAM (only if the patients received AAM) until receiving AAM (matching with replacement).[8–10] We set the caliper width for the nearest neighbor matching at 0.2 SD of the propensity scores in the logit scale.[20,21] To assess the performance of the risk-set matching, we calculated a standardized difference for each covariate. We regarded standardized difference <0.25 as a well-matched balance.[21]

In each matched cohort of initial rhythms, to evaluate the timing effect of AAM, we fitted log link function in generalized estimating equations to estimate risk ratios (RRs) with 95% CIs.[22] The model included the interval from the initiation of EMS CPR to matching as a categorical variable by 5 minutes. We used generalized estimating equations to address potential correlation within-pair of risk-set matching.[20] We used frequency weighting adjustment to account for the number of the duplications between patients AAM and at-risk patients because some patients could have been duplicated in AAM group and at-risk group (ie, patients matched as at risk of receiving AAM could have been matched as at-risk patients again or patients receiving AAM later [if the patients received AAM later]).[21] Using the matched cohorts, we repeated the log link function in generalized estimating equations, stratifying AAM into SGA and ETI as stratified analyses. All statistical analyses were performed with R software, version 3.5.1 (www.r-project.org).

RESULTS

We observed 499 944 patients with OHCA from 2014 through 2017 in Japan (Figure 1). Using the described inclusion and exclusion criteria, 424 260 patients were eligible for our study. A total of 27 957 patients (6.6%) had shockable and 396 303 (93.4%) had nonshockable rhythms.

We present patient characteristics in each cohort of initial rhythms in Table 1. There were 11 390 patients (40.7%) with initial shockable rhythms and 164 040 patients (41.4%) with initial nonshockable rhythms who received AAM during CPR. The median interval between the initiation of EMS CPR and AAM was 8 minutes (IQR, 5–12 minutes) in both rhythms.

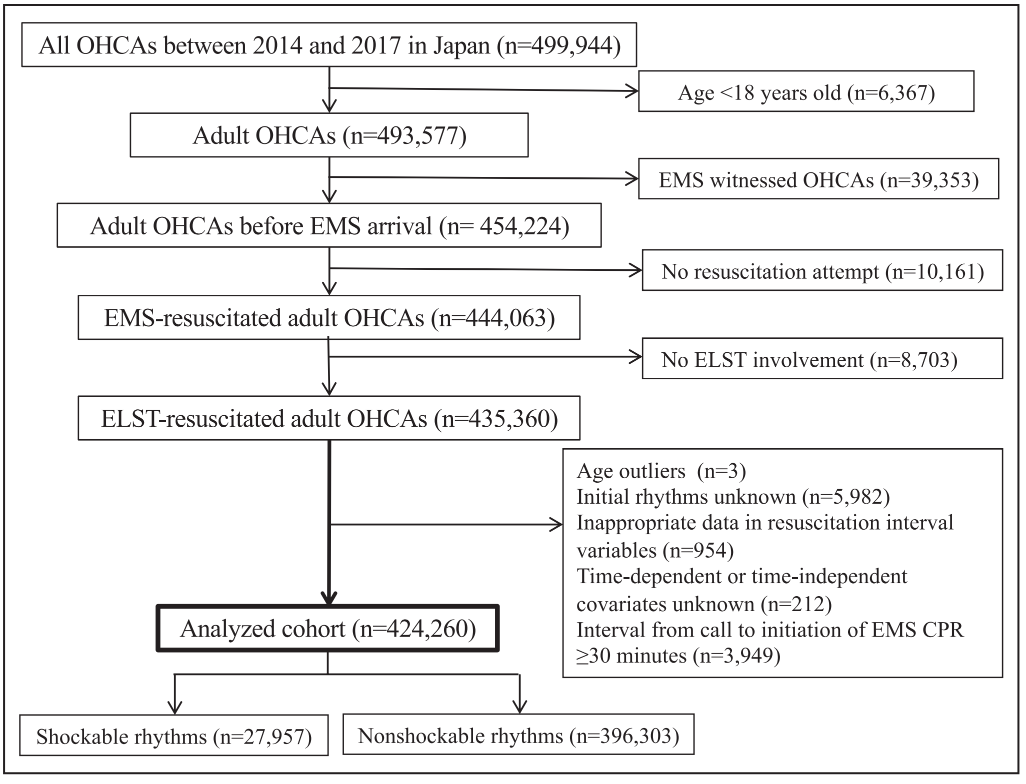


Figure 1. Study participant flowchart.
CPR indicates cardiopulmonary resuscitation; ELST, emergency life-saving technician; EMS, emergency medical services; and OHCA, out-of-hospital cardiac arrest.

Using risk-set matching, 11 306 patients who received AAM in the cohort of shockable rhythms and 163 796 patients who received AAM in the cohort of nonshockable rhythms were matched with at-risk patients (Table 2). Among those matched as at-risk patients in the shockable and nonshockable cohorts, 3899 (34.5%) and 49 415 (30.2%), respectively, received AAM after the matching. In both cohorts, standardized differences were within 0.25 for all covariates, indicating good postmatching balance. In the shockable cohort, median intervals between the initiation of EMS CPR and AAM were 8 minutes (IQR, 5–11 minutes) for the AAM group and 11 minutes (IQR, 8–15 minutes) for the at-risk group. In the nonshockable cohort, median intervals between the initiation of EMS CPR and AAM were 8 minutes (IQR, 5–12 minutes) for the AAM group and 11 minutes (IQR, 8–15 minutes) for the at-risk group. In the shockable cohort, patients who ever received epinephrine were 5422 (48.0%) for the AAM group and 4272 (37.8%) for the at-risk group. In the nonshockable cohort, patients who ever received epinephrine were 49 863 (30.4%) for the AAM group and 32 969 (20.1%) for the at-risk group.

We present the estimated effect size of AAM by the timing of AAM in the shockable cohort in Figure 2. Compared with at-risk of receiving AAM, the RRs of AAM on 1-month survival were 1.01 (95% CI, 0.89–1.15) between 0 and 5 minutes, 1.06 (95% CI, 0.98–1.15) between 5 and 10 minutes, 0.99 (95% CI, 0.87–1.12) between 10 and 15 minutes, 0.74 (95% CI, 0.59–0.92) between 15 and 20 minutes, 0.61 (95% CI, 0.37–1.00) between 20 and 25 minutes, and 0.73 (95% CI, 0.26–2.07) between 25 and 30 minutes after the initiation of EMS CPR (Figure 2A). The RRs of AAM on 1-month survival with favorable functional status by the timing of AAM are shown in Figure 2B.

We present the estimated effect size of AAM by the timing of AAM in the nonshockable cohort in Figure 3. The RRs of AAM on 1-month survival were 1.12 (95% CI, 1.00–1.27) between 0 and 5 minutes, 1.34 (95% CI, 1.25–1.44) between 5 and 10 minutes, 1.39 (95% CI, 1.26–1.54) between 10 and 15 minutes, 1.20 (95% CI, 0.99–1.45) between 15 and 20 minutes, 1.18 (95% CI, 0.80–1.73) between 20 and 25 minutes, 0.63 (95% CI, 0.29–1.38) between 25 and 30 minutes, and 0.44 (95% CI, 0.11–1.69) at >30 minutes after the initiation of EMS CPR (Figure 3A). The RRs of AAM on 1-month survival with favorable functional status by the timing of AAM are shown in Figure 3B. We show results of the stratified analyses in Figures S1 through S4.

DISCUSSION

In this secondary analysis of the prospective, nationwide, population-based OHCA registry in Japan using time-dependent propensity score and risk-set matching analyses, we did not detect an optimal timing of AAM that was associated with improved 1-month survival for adult patients with shockable rhythms, but found that AAM within 15 minutes after the initiation of EMS CPR was associated with improved 1-month survival for patients with nonshockable rhythms. We also did not observe favorable timing of AAM on 1-month survival with favorable functional status for those with both shockable and nonshockable rhythms.

Comparison With Prior Studies

Several studies reported an association between early AAM and favorable patient outcomes. We previously analyzed a population-based OHCA registry in Osaka, Japan and found that AAM between 0 and 4 minutes after the initiation of EMS CPR was associated with a higher likelihood of 1-month survival (adjusted odds ratio [OR] 1.42 [95% CI, 1.23–1.65]), compared with AAM between 5 and 29 minutes after the initiation of EMS CPR.[23] An observational study in King County in Washington State, United States including 693 patients with layperson-witnessed OHCA from 1991 through 2003 demonstrated that late ETI (≥13 minutes after witnessed collapse) was associated with a lower likelihood of survival to hospital discharge (adjusted OR, 0.42 [95% CI, 0.26–0.69]), compared with early ETI (≤12 minutes after witnessed collapse).[24] Most recently, an observational study of the Resuscitation Outcomes Consortium Prehospital Resuscitation using an Impedance Valve and Early versus Delayed trial including >7500 layperson-witnessed OHCA between 2007 and 2010 in the United States and Canada also reported that each additional minute from EMS arrival to successful AAM was associated with a decreased chance of survival to hospital discharge for shockable (adjusted OR, 0.91 [95% CI, 0.89–0.93]) and nonshockable rhythms (adjusted OR, 0.89 [95% CI, 0.85–0.92]).[25]

Strengths of This Study

Prior knowledge supported an association between early AAM and favorable patient outcomes after OHCA. However, resuscitation time bias likely affected the conclusions.[6] Because time to AAM is correlated with resuscitation duration—those with late AAM tend to have longer resuscitation duration before ROSC than those with early AAM; resuscitation time bias skews the timing effect of AAM toward favoring early AAM.[6] Using time-dependent propensity score and risk-set matching analyses, we accounted for resuscitation time bias and expand prior knowledge with more robust methodologies.

The estimated magnitude of the relative risks in our study should be interpreted as the ratio of the risk of outcomes with AAM at the time of matching, compared with

Table 2. Characteristics of Adult Patients With Out-of-Hospital Cardiac Arrest With AAM and at Risk of Receiving AAM in Time-Dependent Propensity Score–Matched Cohort

Characteristics	Shockable rhythms			Nonshockable rhythms		
	At risk of receiving AAM (n=11 306)	AAM (n=11 306)	Standardized differences	At risk of receiving AAM (n=163 796)	AAM (n=163 796)	Standardized differences
Patient demographics						
Age, median (IQR), y	69 (58–79)	69 (59–79)	0.005	80 (70–87)	80 (70–87)	0.005
Sex, n (%)			0.014			0.002
Male	8920 (78.9)	8857 (78.3)		92 780 (56.6)	92 634 (56.6)	
Arrest characteristics						
Year of arrest, n (%)			0.014			0.001
2014	2880 (25.5)	2907 (25.7)		41 022 (25.0)	41 014 (25.0)	
2015	2740 (24.2)	2724 (24.1)		40 677 (24.8)	40 675 (24.8)	
2016	2835 (25.1)	2780 (24.6)		40 077 (24.5)	40 129 (24.5)	
2017	2851 (25.2)	2895 (25.6)		42 020 (25.7)	41 978 (25.6)	
Season of arrest, n (%)			0.012			0.007
Spring	2706 (23.9)	2719 (24.0)		39 990 (24.4)	40 386 (24.7)	
Summer	2471 (21.9)	2511 (22.2)		30 101 (18.4)	30 212 (18.4)	
Fall	2646 (23.4)	2650 (23.4)		37 532 (22.9)	37 229 (22.7)	
Winter	3483 (30.8)	3426 (30.3)		56 173 (34.3)	55 969 (34.2)	
Day of arrest, n (%)			0.002			0.001
Weekday (Monday to Friday)	9655 (85.4)	9661 (85.5)		141 248 (86.2)	141 173 (86.2)	
Weekend (Saturday and Sunday)	1651 (14.6)	1645 (14.5)		22 548 (13.8)	22 623 (13.8)	
Time of arrest, n (%)			0.003			0.005
Daytime (9:00–16:59)	3777 (33.4)	3795 (33.6)		55 837 (34.1)	55 450 (33.9)	
Nighttime (17:00–8:59)	7529 (66.6)	7511 (66.4)		107 959 (65.9)	108 346 (66.1)	
Quartiles of prefecture preference for performing AAM			0.016			0.007
Quartile 1 (shockable: <24.2%) (nonshockable: <26.6%)	1215 (10.7)	1181 (10.4)		18 396 (11.2)	18 476 (11.3)	
Quartile 2 (shockable: 24.4%–35.2%) (nonshockable: 26.6%–38.9%)	1437 (12.7)	1433 (12.7)		21 149 (12.9)	21 085 (12.9)	
Quartile 3 (Shockable: 35.2%–48.3%) (Nonshockable: 38.9%–53.2%)	3020 (26.7)	2976 (26.3)		48 909 (29.9)	48 560 (29.6)	
Quartile 4 (shockable: >48.3%) (nonshockable: >53.2%)	5634 (49.8)	5716 (50.6)		75 342 (46.0)	75 675 (46.2)	
Cause, n (%)			0.004			0.003
Medical	11 063 (97.9)	11 056 (97.8)		147 409 (90.0)	147 248 (89.9)	
Nonmedical	243 (2.1)	250 (2.2)		16 387 (10.0)	16 548 (10.1)	
Witness status, n (%)			0.029			0.008
Unwitnessed	3413 (30.2)	3551 (31.4)		106 280 (64.9)	105 783 (64.6)	
By family	4973 (44.0)	4933 (43.6)		36 212 (22.1)	36 585 (22.3)	
By friend	635 (5.6)	604 (5.3)		2018 (1.2)	2077 (1.3)	
By colleague	662 (5.9)	651 (5.8)		1171 (0.7)	1235 (0.8)	

(Continued)

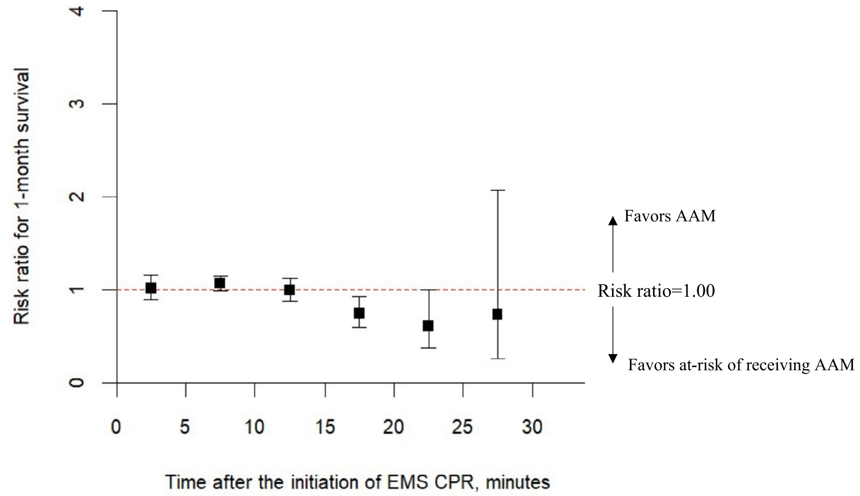
Table 2. Continued

Characteristics	Shockable rhythms			Nonshockable rhythms		
	At risk of receiving AAM (n=11 306)	AAM (n=11 306)	Standardized differences	At risk of receiving AAM (n=163 796)	AAM (n=163 796)	Standardized differences
By passerby	515 (4.6)	501 (4.4)		1923 (1.2)	1940 (1.2)	
By others	1108 (9.8)	1066 (9.4)		16 192 (9.9)	16 176 (9.9)	
Initial rhythms, n (%)			N/A			0.008
PEA	N/A	N/A		38 643 (23.6)	39 171 (23.9)	
Asystole	N/A	N/A		125 153 (76.4)	124 625 (76.1)	
Layperson interventions						
Layperson CPR, n (%)			0.011			0.002
Chest compression only CPR	5638 (49.9)	5594 (49.5)		78 521 (47.9)	78 482 (47.9)	
Chest compression with ventilation	746 (6.6)	729 (6.4)		9925 (6.1)	9995 (6.1)	
No layperson CPR	4922 (43.5)	4983 (44.1)		75 350 (46.0)	75 319 (46.0)	
Public access AED shock delivery, n (%)	469 (4.1)	467 (4.1)	0.001	1433 (0.9)	1429 (0.9)	<0.001
EMS interventions						
Dispatcher CPR instruction, n (%)	6623 (58.6)	6656 (58.9)	0.006	104 839 (64.0)	104 727 (63.9)	0.001
Prehospital physician involvement, n (%)	621 (5.5)	620 (5.5)	<0.001	4098 (2.5)	4050 (2.5)	0.002
Interval between emergency call and initiation of EMS CPR, median (IQR), min	9 (7–11)	9 (7–11)	0.022	9 (7–11)	9 (7–11)	0.005
EMS shock delivery before matching, n (%)	10 382 (91.8)	10 221 (90.4)	0.050	2611 (1.6)	2373 (1.4)	0.012
Interval between initiation of EMS CPR and EMS shock delivery, median (IQR), min	1 (1–2)	1 (1–2)	0.054	5 (3–8)	5 (3–8)	0.078
Epinephrine administration before matching, n (%)	1103 (9.8)	1005 (8.9)	0.030	7145 (4.4)	6628 (4.0)	0.016
Interval between initiation of EMS CPR and epinephrine administration, median (IQR), min	9 (7–12.5)	9 (7–13)	0.014	9 (7–13)	9 (7–13)	0.07
Type of AAM			N/A			N/A
SGA	3333 (29.5)	9691 (85.7)		38 179 (23.3)	131 026 (80.0)	
Laryngeal tube	3091 (27.3)	8942 (79.1)		35 839 (21.9)	121 779 (74.3)	
Laryngeal mask	242 (2.1)	749 (6.6)		2340 (1.4)	9247 (5.6)	
ETI	566 (5.0)	1615 (14.3)		11 236 (6.9)	32 770 (20.0)	
Interval between initiation of EMS CPR and AAM, median (IQR), min	11 (8–15)	8 (5–11)	N/A	11 (8–15)	8 (5–12)	N/A

AAM indicates advanced airway management; AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ETI, endotracheal intubation; IQR, interquartile range; N/A, not applicable; PEA, pulseless electrical activity; and SGA supraglottic airway.

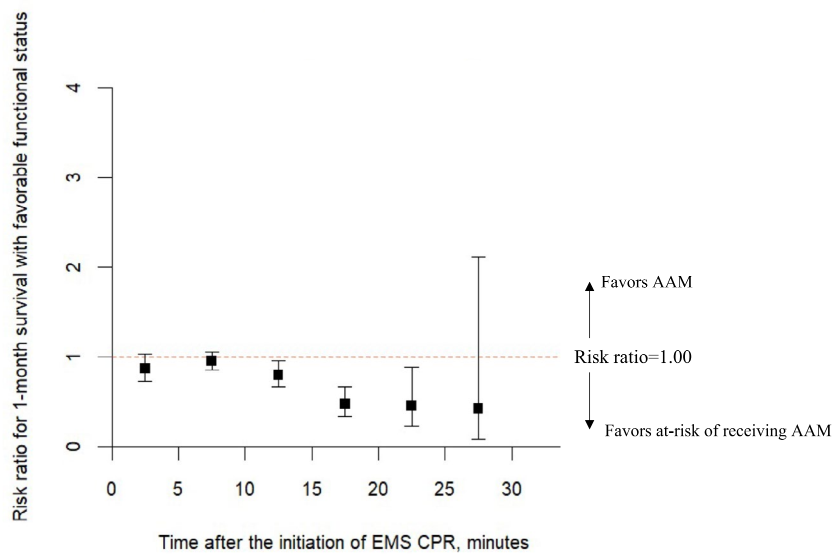
the risk of outcomes without AAM at the same minute. This interpretation addresses a clinical question, "Would AAM be beneficial now, compared with not now?" Our study matched a patient with AAM to another patient without AAM at the same minute who could have received AAM later or who did not receive AAM at all. Since EMS providers are unaware whether the future event will occur or not (ie, subsequently receiving AAM

A



Time after the initiation of EMS CPR, minutes	0-5	5-10	10-15	15-20	20-25	25-30	>30
AAM	365/1353 (27.0%)	1225/5012 (24.4%)	460/3091 (14.9%)	127/1257 (10.1%)	24/432 (5.6%)	6/140 (4.3%)	0/21 (0%)
At-risk of receiving AAM	363/1353 (26.8%)	1156/5012 (23.1%)	495/3091 (16.0%)	172/1257 (13.7%)	40/432 (9.3%)	9/140 (6.4%)	0/21 (0%)
Risk ratio (95% CI)	1.01 (0.89-1.15)	1.06 (0.98-1.15)	0.99 (0.87-1.12)	0.74 (0.59-0.92)	0.61 (0.37-1.00)	0.73 (0.26-2.07)	*

B

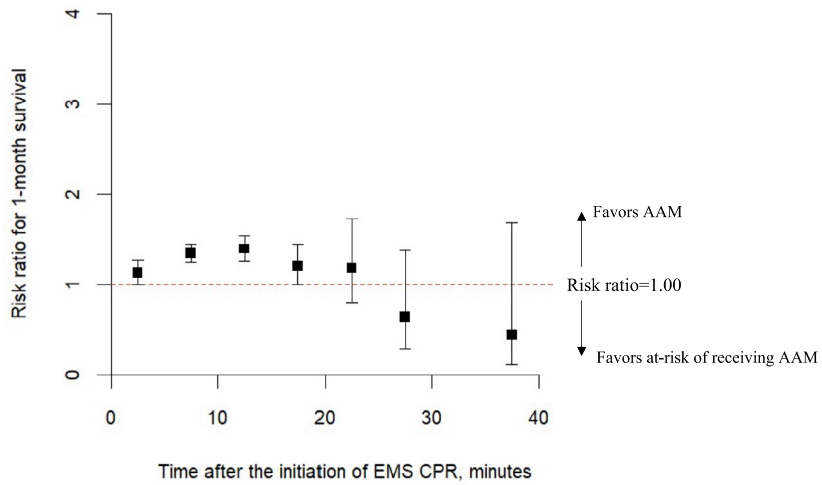


Time after the initiation of EMS CPR, minutes	0-5	5-10	10-15	15-20	20-25	25-30	>30
AAM	209/1353 (15.4%)	647/5012 (12.9%)	206/3091 (6.7%)	48/1257 (3.8%)	12/432 (2.8%)	2/140 (1.4%)	0/21 (0%)
At-risk of receiving AAM	243/1353 (18.0%)	693/5012 (13.8%)	279/3091 (9.0%)	95/1257 (7.6%)	26/432 (6.0%)	5/140 (3.6%)	0/21 (0%)
Risk ratio (95% CI)	0.87 (0.73-1.03)	0.95 (0.85-1.05)	0.79 (0.66-0.95)	0.47 (0.33-0.67)	0.45 (0.23-0.88)	0.42 (0.08-2.11)	*

Figure 2. Association between timing of advanced airway management and 1-month survival (A) and 1-month survival with favorable functional status (B) for patients with shockable rhythms.

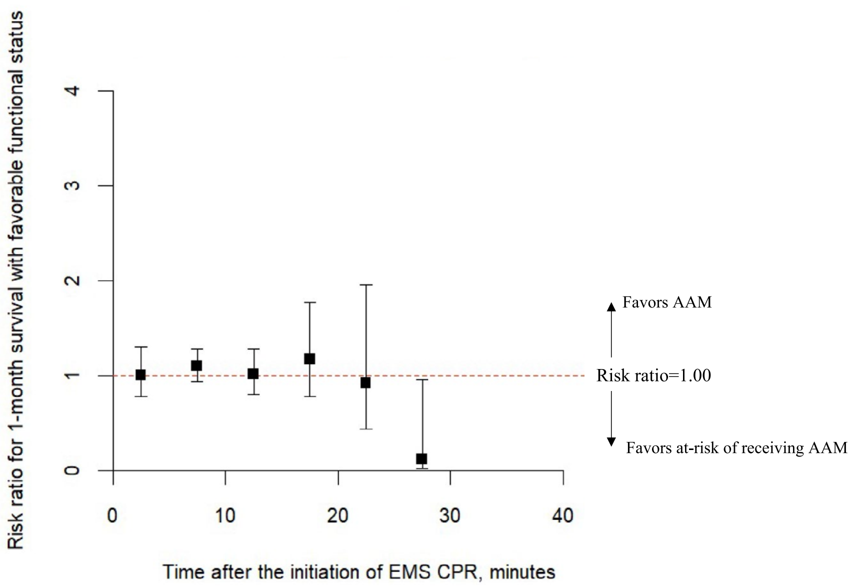
Box plots indicate point estimates of treatment effects of AAM with 95% CIs. AAM indicates advanced airway management; CPR, cardiopulmonary resuscitation; and EMS, emergency medical services. *The model did not converge.

A



Time after the initiation of EMS CPR, minutes	0-5	5-10	10-15	15-20	20-25	25-30	>30
AAM	568/21878 (2.6%)	1916/68845 (2.8%)	980/45547 (2.2%)	254/18594 (1.4%)	60/6159 (1.0%)	11/1953 (0.6%)	3/820 (0.4%)
At-risk of receiving AAM	507/21878 (2.3%)	1392/68845 (2.0%)	684/45547 (1.5%)	214/18594 (1.2%)	51/6159 (0.8%)	16/1953 (0.8%)	7/820 (0.9%)
Risk ratio (95% CI)	1.12 (1.00-1.27)	1.34 (1.25-1.44)	1.39 (1.26-1.54)	1.20 (0.99-1.45)	1.18 (0.80-1.73)	0.63 (0.29-1.38)	0.44 (0.11-1.69)

B



Time after the initiation of EMS CPR, minutes	0-5	5-10	10-15	15-20	20-25	25-30	>30
AAM	121/21878 (0.6%)	357/68845 (0.5%)	154/45547 (0.3%)	51/18594 (0.3%)	14/6159 (0.2%)	1/1953 (0.1%)	0/820 (0%)
At-risk of receiving AAM	122/21878 (0.6%)	330/68845 (0.5%)	152/45547 (0.3%)	45/18594 (0.2%)	14/6159 (0.2%)	7/1953 (0.4%)	3/820 (0.4%)
Risk ratio (95% CI)	1.01 (0.78-1.30)	1.09 (0.93-1.28)	1.01 (0.80-1.28)	1.17 (0.77-1.77)	0.92 (0.43-1.95)	0.12 (0.01-0.95)	*

Figure 3. Association between timing of advanced airway management and 1-month survival (A) and 1-month survival with favorable functional status (B) for patients with nonshockable rhythms.

Box plots indicate point estimates of treatment effects of AAM with 95% CIs. AAM indicates advanced airway management; CPR, cardiopulmonary resuscitation; and EMS, emergency medical services. *The model did not converge.

or not after 1 time point), this estimated magnitude of the association in our study is clinically relevant.

Implications

For nonshockable rhythms, our study findings showed the association of early AAM (within 15 minutes after the initiation of EMS CPR) with improved 1-month survival. The results may support early AAM for nonshockable rhythms. However, the association was not observed for favorable functional recovery. Rare outcome event might have contributed to the nonsignificant estimated effect sizes of AAM on functional outcome. We should note that survival and neurological outcomes in this study appear to be lower than those in North America.[1,26] The possible reasons for the outcome difference include the older patient population in Japan and the difference in the proportion of patients who receive resuscitation attempts among EMS-assessed OHCAs. The Resuscitation Outcomes Consortium, a multicenter OHCA research network in the United States and Canada, reported that 55.6% of EMS-assessed OHCAs received resuscitation attempts,[26] while 98.2% of EMS-assessed OHCA received resuscitation attempts in Japan, which suggest that a less selective patient population underwent resuscitation attempts in Japan and could have contributed to the lower patient outcomes.[27]

For shockable rhythms, we did not observe a statistically significant association of early AAM with 1-month survival. The difference in underlying causes between shockable and nonshockable rhythms could explain the difference in the responses to early AAM between the rhythms.[28] However, regarding functional recovery, we observed that AAM was associated with a decreased chance of favorable functional outcome between 10 and 25 minutes for patients with shockable rhythms. This may not support AAM after 10 minutes from EMS CPR for shockable rhythms. Our findings highlight the importance of personalized medical care for cardiac arrest and provide more evidence to the current AHA Guidelines' recommendation.[3]

Another implication to clinical researchers is that our results generated clinical equipoise that justifies future clinical trials to evaluate the optimal timing of AAM. Although 2 recent trials in the United States and the United Kingdom compared SGA versus ETI for OHCA, the ideal timing of AAM remains unclear.[29,30] Since our study is an observational design and cannot evaluate causality, future trials would be indicated.

Limitations

First, the numbers of attempted AAM and failed AAM were not available in the registry. Failed AAM might have counted as at risk of receiving AAM and could have biased the results. Second, the timing of AAM may be a surrogate of EMS systems performance (ie, high-performing EMS systems may conduct AAM early). Although accounting for clustering of patients within EMS systems would have addressed this limitation, the data set did not include information on EMS systems and we were unable to adjust for the clustering. Similarly, we were unable to adjust for unmeasured confounding factors such as patient comorbidities, chest compression metrics, and postresuscitation practice (eg, targeted temperature management and coronary reperfusion therapy) since the registry did not capture these variables. Third, this is an observational study that limits the ability to infer causation, and we only report an association. Fourth, the findings may not be externally valid at other EMS systems. Lastly, as with all epidemiological studies, data integrity, validity, reliability, and ascertainment bias are potential limitations. For example, although a prior study showed substantially high inter-rater reliability of CPC scale,[31] inter-rater reliability of CPC in our study setting is unknown. The use of uniform data collection with Utstein template for reporting cardiac arrest, nationwide large sample size, and a population-based design to cover all patients with OHCA in Japan was intended to minimize these potential limitations.

CONCLUSIONS

In this observational study including >420 000 adult patients with OHCA in Japan, we found that the timing of AAM was not statistically associated with improved 1-month survival for shockable rhythms, but AAM within 15 minutes after the initiation of CPR by EMS providers was associated with improved 1-month survival for nonshockable rhythms.

ARTICLE INFORMATION

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Author Contributions: Drs Okubo and Komukai had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: All authors; Acquisition, analysis, or interpretation of data: Author contributions: All authors; Drafting of the manuscript: Okubo; Critical revision of the manuscript: All authors; Statistical analysis: Komukai, Izawa, Gibo; Study supervision: Iwami, Callaway, Kitamura. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Disclosures

None.

Supplementary Materials

Data S1
Figures S1–S4
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Supplemental Material

Data S1.

Supplemental Methods

Emergency Medical Services (EMS) System in Japan

In Japan, municipal governments provide EMS systems through local fire departments, and there were 752 fire departments with dispatch centers in 2014.[13] All EMS providers perform resuscitation according to the Japanese cardiopulmonary resuscitation (CPR) guideline, based on the International Liaison Committee on Resuscitation consensus.[32] EMS providers initiate resuscitation except particular conditions (e.g., decapitation, incineration, decomposition, rigor mortis, or dependent cyanosis) and are not legally permitted to terminate resuscitation in the field.[9,10,13] The majority of EMS-treated out-of-hospital cardiac arrest (OHCA) patients are therefore transferred to hospitals and included in the registry.

Prehospital advanced airway management in Japan

Each ambulance crew consists of 3 EMS providers, including at least 1 emergency life-saving technician (ELST), specially trained EMS providers. Under on-line medical direction, ELSTs are authorized to insert an intravenous line, administer epinephrine, and perform insertion of supraglottic airway device (SGA) only for patients with OHCA.[9]

SGAs such as laryngeal tubes or laryngeal masks have been used in Japan since 1991.[9] Since 2004, certified ELSTs have been permitted to perform endotracheal intubation (ETI) under on-line medical direction after completion of additional training as described below.[9,10] Certified ELSTs are allowed to perform ETI only during cardiac arrest (i.e., not allowed to intubate after return of spontaneous circulation [ROSC]). To become a certified ELST who is able to perform

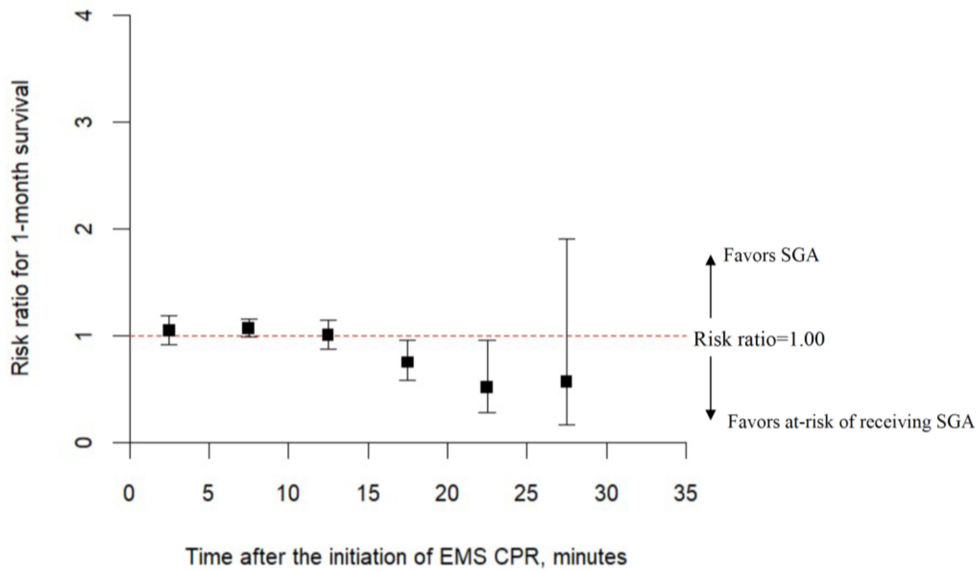
ETI, each ELST must complete training that is authorized by a regional medical control committee.[9,10] The training period is more than 62 terms, and each term consists of 50 minutes session.[33,34] The practical training includes more than 30 successful intubations at operating rooms under the guidance and supervision of attending physicians.[33,34] When ELSTs place advanced airway for patients with OHCA, standard ELSTs can use only SGAs, while certified ELSTs can select either SGAs or ETI at the discretion of each certified ELST under on-line medical direction.

Data collection and quality control

All-Japan Utstein Registry prospectively collected EMS assessed OHCA, using the Utstein Resuscitation Registry Templates for OHCA.[11,12,14] The form includes age, sex, date of cardiac arrest, etiology of cardiac arrest, onset witnessed by layperson, first documented rhythm, presence and type of layperson CPR (chest-compression-only CPR without rescue breathing or conventional CPR with rescue breathing), presence of dispatcher CPR instruction, public-access AEDs shock delivery, presence and type of prehospital advanced airway management (AAM), prehospital administration of intravenous fluids and epinephrine, and resuscitation time-course, as well as outcome measures, including prehospital ROSC, 1-month survival, and functional status at 1 month after the arrest.[9,10,13,15,27] The resuscitation time-course variables included each time of receipt of an emergency call, initiation of CPR by EMS providers, defibrillation by EMS providers, epinephrine administration, prehospital ROSC, successful placement of advanced airway device by EMS providers, and hospital arrival. Specifically, the time data of successful placement of advanced airway device is available after January 2014, and this enabled to account for the timing of AAM in our study. These resuscitation time-course variables were recorded according to the time on the clock used by each EMS system. All survivors were followed for up to 1 month after the OHCA by the EMS providers who had provided the prehospital care.[35] Functional outcome was determined by the physician who were responsible for the care of the patient by a follow-up interview 1 month after successful resuscitation with the Cerebral Performance Category scale.[35] The data were integrated into the registry system on the Fire and Disaster Management Agent (FDMA) database server, and subsequently had logical checks by the computer-operated system. When the data form was not completed, the FDMA contacted the respective EMS and instructed them to complete the form.

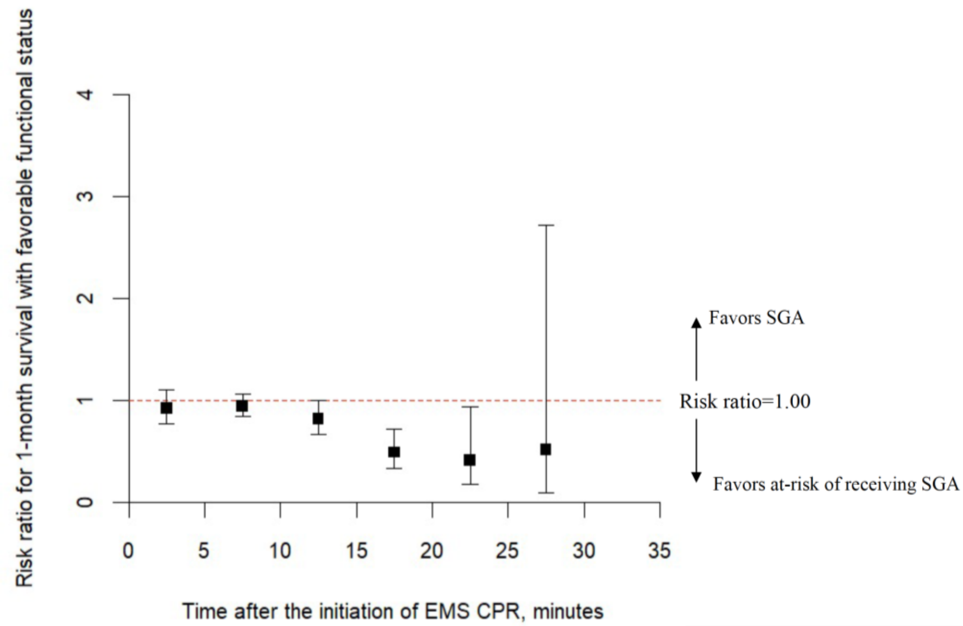
Figure S1. **Association between timing of supraglottic airway insertion and 1-month survival (A) and 1-month survival with favorable functional status (B) for patients with shockable rhythms. Box plots indicate point estimates of treatment effects of SGA with 95% CIs.**

A



Time after the initiation of EMS CPR, minutes	**0-5**	**5-10**	**10-15**	**15-20**	**20-25**	**25-30**	**>30**
SGA	341/1229 (27.7%)	1096/4436 (24.7%)	381/2559 (14.9%)	100/1004 (10.0%)	14/338 (4.1%)	4/110 (3.6%)	0/15 (0%)
At-risk of receiving SGA	330/1229 (26.9%)	1023/4436 (23.1%)	402/2559 (15.7%)	136/1004 (13.5%)	28/338 (8.3%)	8/110 (7.3%)	0/15 (0%)
Risk ratio (95% CI)	1.04 (0.91-1.19)	1.07 (0.98-1.16)	1.00 (0.87-1.15)	0.75 (0.58-0.96)	0.52 (0.28-0.96)	0.57 (0.17-1.91)	*

B

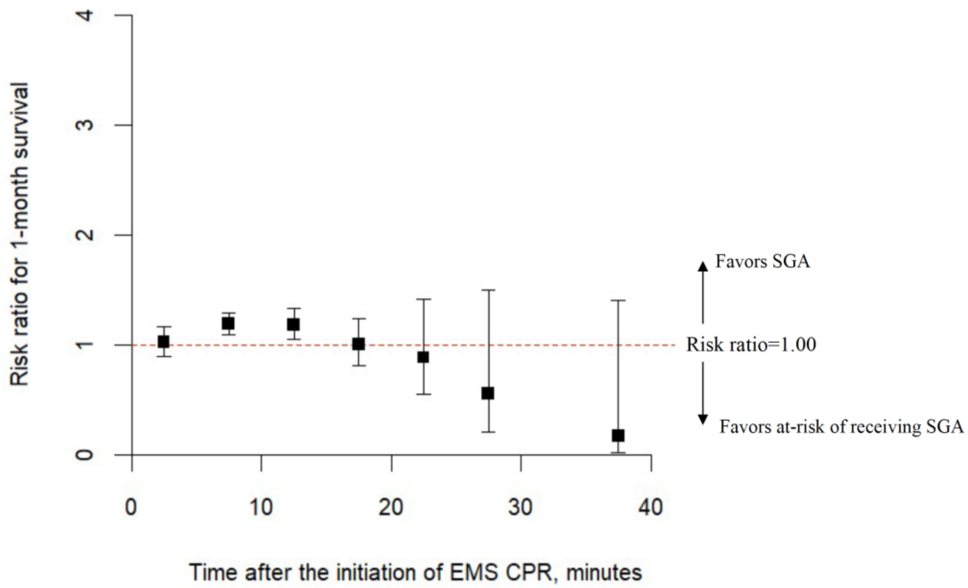


Time after the initiation of EMS CPR, minutes	0-5	5-10	10-15	15-20	20-25	25-30	>30
SGA	195/1229 (15.9%)	583/4436 (13.1%)	174/2559 (6.8%)	38/1004 (3.8%)	7/338 (2.1%)	2/110 (1.8%)	0/15 (0%)
At-risk of receiving SGA	214/1229 (17.4%)	619/4436 (14.0%)	230/2559 (9.0%)	76/1004 (7.6)	18/338 (5.3%)	4/110 (3.6%)	0/15 (0%)
Risk ratio (95% CI)	0.92 (0.77-1.10)	0.94 (0.84-1.06)	0.81 (0.67-0.99)	0.49 (0.33-0.71)	0.40 (0.17-0.94)	0.51 (0.10-2.72)	*

* The model did not converge.
CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; SGA, supraglottic airway.

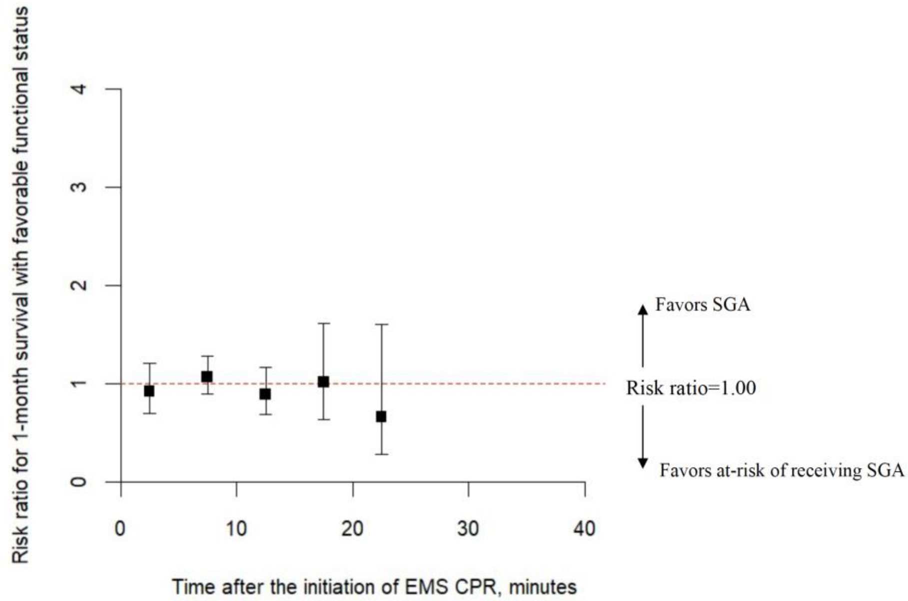
Figure S2. **Association between timing of supraglottic airway insertion and 1-month survival (A) and 1-month survival with favorable functional status (B) for patients with nonshockable rhythms. Box plots indicate point estimates of treatment effects of SGA with 95% CIs.**

A.



Time after the initiation of EMS CPR, minutes	**0-5**	**5-10**	**10-15**	**15-20**	**20-25**	**25-30**	**>30**
SGA	457/19431 (2.4%)	1370/56792 (2.4%)	652/34994 (1.9%)	173/13597 (1.3%)	34/4310 (0.8%)	6/1334 (0.4%)	1/568 (0.2%)
At-risk of receiving SGA	449/19431 (2.3%)	1141/56792 (2.0%)	544/34994 (1.6%)	172/13597 (1.3%)	38/4310 (0.9%)	11/1334 (0.8%)	6/568 (1.1%)
Risk ratio (95% CI)	1.02 (0.90-1.16)	1.19 (1.09-1.29)	1.18 (1.05-1.33)	1.00 (0.81-1.24)	0.88 (0.55-1.42)	0.56 (0.21-1.50)	0.17 (0.02-1.40)

B.

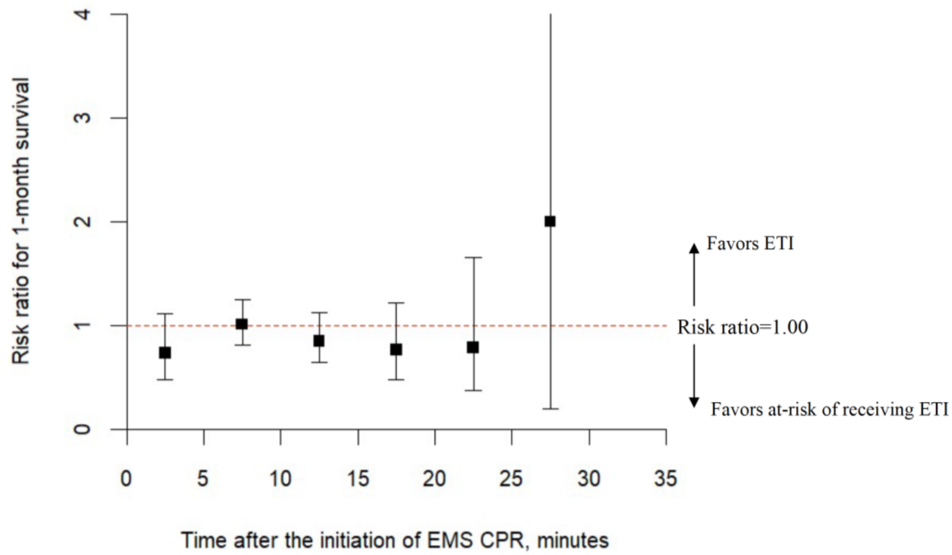


Time after the initiation of EMS CPR, minutes	0-5	5-10	10-15	15-20	20-25	25-30	>30
SGA	98/19431 (0.5%)	275/56792 (0.5%)	110/34994 (0.3%)	37/13597 (0.3%)	9/4310 (0.2%)	0/1334 (0%)	0/568 (0%)
At-risk of receiving SGA	110/19431 (0.6%)	261/56792 (0.5%)	122/34994 (0.3%)	37/13597 (0.3%)	12/4310 (0.3%)	5/1334 (0.4%)	2/568 (0.4%)
Risk ratio (95% CI)	0.92 (0.69-1.21)	1.07 (0.89-1.27)	0.89 (0.68-1.17)	1.01 (0.63-1.61)	0.66 (0.27-1.60)	*	*

* The model did not converge.
CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; SGA, supraglottic airway.

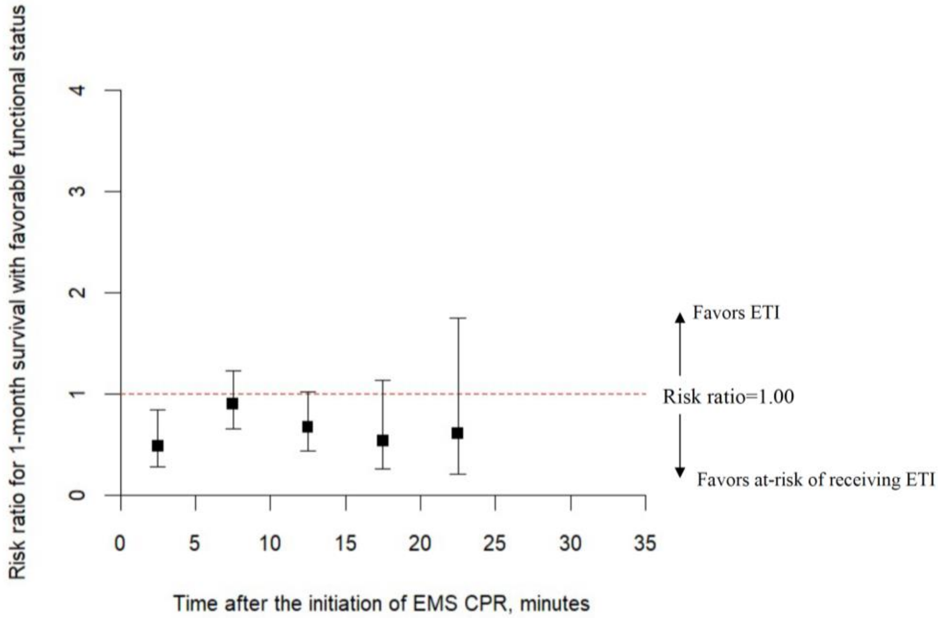
Figure S3. **Association between timing of endotracheal intubation and 1-month survival (A) and 1-month survival with favorable functional status (B) for patients with shockable rhythms. Box plots indicate point estimates of treatment effects of ETI with 95% CIs.**

A.



Time after the initiation of EMS CPR, minutes	0-5	5-10	10-15	15-20	20-25	25-30	>30
ETI	24/124 (19.4%)	129/576 (22.4%)	79/532 (14.8%)	27/253 (10.7%)	10/94 (10.6%)	2/30 (6.7%)	0/6 (0%)
At-risk of receiving ETI	33/124 (26.6%)	133/576 (23.1%)	93/532 (17.5%)	36/253 (14.2%)	12/94 (12.8%)	1/30 (3.3%)	0/6 (0%)
Risk ratio (95% CI)	0.73 (0.48-1.11)	1.01 (0.81-1.25)	0.85 (0.64-1.12)	0.76 (0.48-1.22)	0.78 (0.37-1.65)	2.00 (0.19-20.66)	*

B.

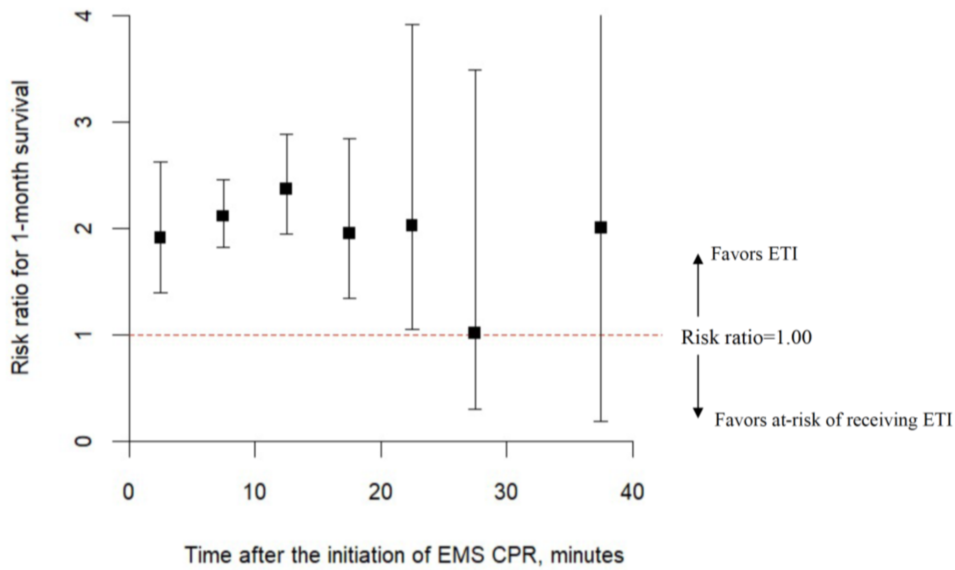


Time after the initiation of EMS CPR, minutes	0-5	5-10	10-15	15-20	20-25	25-30	>30
ETI	14/124 (11.3%)	64/576 (11.1%)	32/532 (6.0%)	10/253 (4.0%)	5/94 (5.3%)	0/30 (0%)	0/6 (0%)
At-risk of receiving ETI	29/124 (23.4%)	74/576 (12.8%)	49/532 (9.2%)	19/253 (7.5%)	8/94 (8.5%)	1/30 (3.3%)	0/6 (0%)
Risk ratio (95% CI)	0.48 (0.28-0.84)	0.90 (0.65-1.23)	0.67 (0.43-1.02)	0.53 (0.25-1.13)	0.60 (0.21-1.74)	*	*

* The model did not converge.
CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; ETI, endotracheal intubation.

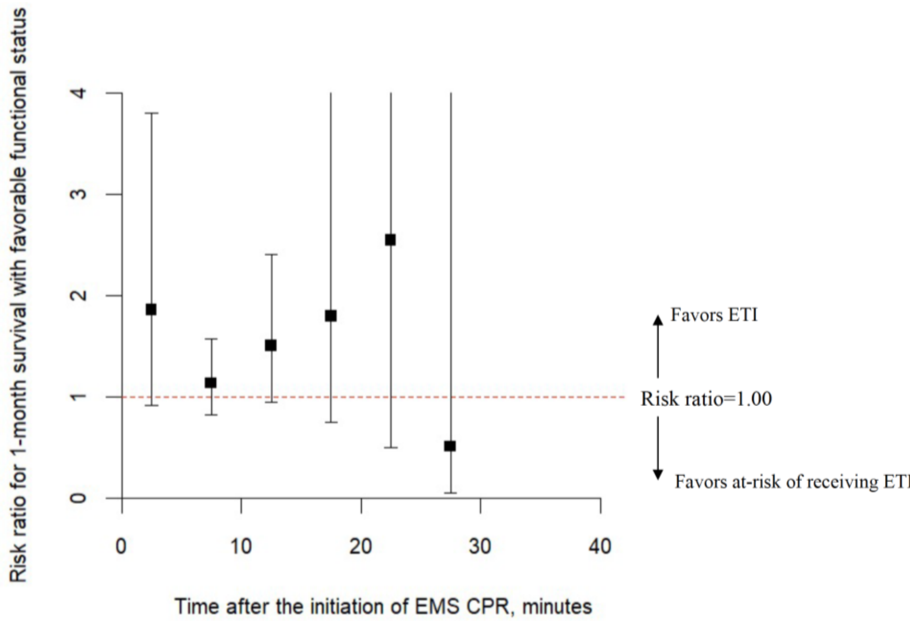
Figure S4. **Association between timing of endotracheal intubation and 1-month survival (A) and 1-month survival with favorable functional status (B) for patients with nonshockable rhythms. Box plots indicate point estimates of treatment effects of ETI with 95% CIs.**

A.



Time after the initiation of EMS CPR, minutes	**0-5**	**5-10**	**10-15**	**15-20**	**20-25**	**25-30**	**>30**
ETI	111/2447 (4.5%)	546/12053 (4.5%)	328/10553 (3.1%)	81/4997 (1.6%)	26/1849 (1.4%)	5/619 (0.8%)	2/252 (0.8%)
At-risk of receiving ETI	58/2447 (2.4%)	251/12053 (2.1%)	140/10553 (1.3%)	42/4997 (0.8%)	13/1849 (0.7%)	5/619 (0.8%)	1/252 (0.4%)
Risk ratio (95% CI)	1.91 (1.39-2.62)	2.11 (1.82-2.46)	2.37 (1.94-2.89)	1.95 (1.34-2.84)	2.02 (1.05-3.91)	1.01 (0.29-3.48)	2.00 (0.18-21.91)

B.



Time after the initiation of EMS CPR, minutes	0-5	5-10	10-15	15-20	20-25	25-30	>30
ETI	23/2447 (0.9%)	82/12053 (0.7%)	44/10553 (0.4%)	14/4997 (0.3%)	5/1849 (0.3%)	1/619 (0.2%)	0/252 (0%)
At-risk of receiving ETI	12/2447 (0.5%)	69/12053 (0.6%)	30/10553 (0.3%)	8/4997 (0.2%)	2/1849 (0.1%)	2/619 (0.3%)	1/252 (0.4%)
Risk ratio (95% CI)	1.86 (0.91-3.80)	1.13 (0.82-1.57)	1.50 (0.94-2.41)	1.79 (0.75-4.26)	2.55 (0.49-13.11)	0.51 (0.05-5.57)	*

* The model did not converge.
CPR indicates cardiopulmonary resuscitation; EMS, emergency medical services; ETI, endotracheal intubation.