Association of Prehospital Advanced Airway Management With Neurologic Outcome and Survival in Patients With Out-of-Hospital Cardiac Arrest

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Importance It is unclear whether advanced airway management such as endotracheal intubation or use of supraglottic airway devices in the prehospital setting improves outcomes following out-of-hospital cardiac arrest (OHCA) compared with conventional bag-valve-mask ventilation.

Objective To test the hypothesis that prehospital advanced airway management is associated with favorable outcome after adult OHCA.

Design, Setting, and Participants Prospective, nationwide, population-based study (All-Japan Utstein Registry) involving 649 654 consecutive adult patients in Japan who had an OHCA and in whom resuscitation was attempted by emergency responders with subsequent transport to medical institutions from January 2005 through December 2010.

Main Outcome Measures Favorable neurological outcome 1 month after an OHCA, defined as cerebral performance category 1 or 2.

Results Of the eligible 649 359 patients with OHCA, 367 837 (57%) underwent bag-valve-mask ventilation and 281 522 (43%) advanced airway management, including 41 972 (6%) with endotracheal intubation and 239 550 (37%) with use of supraglottic airways. In the full cohort, the advanced airway group incurred a lower rate of favorable neurological outcome compared with the bag-valve-mask group (1.1% vs 2.9%; odds ratio [OR], 0.38; 95% CI, 0.36-0.39). In multivariable logistic regression, advanced airway management had an OR for favorable neurological outcome of 0.38 (95% CI, 0.37-0.40) after adjusting for age, sex, etiology of arrest, first documented rhythm, witnessed status, type of bystander cardiopulmonary resuscitation, use of public access automated external defibrillator, epinephrine administration, and time intervals. Similarly, the odds of neurologically favorable survival were significantly lower both for endotracheal intubation (adjusted OR, 0.41; 95% CI, 0.37-0.45) and for supraglottic airways (adjusted OR, 0.38; 95% CI, 0.36-0.40). In a propensity score–matched cohort (357 228 patients), the adjusted odds of neurologically favorable survival were significantly lower both for endotracheal intubation (adjusted OR, 0.45; 95% CI, 0.37-0.55) and for use of supraglottic airways (adjusted OR, 0.36; 95% CI, 0.33-0.39). Both endotracheal intubation and use of supraglottic airways were similarly associated with decreased odds of neurologically favorable survival.

Conclusion and Relevance Among adult patients with OHCA, any type of advanced airway management was independently associated with decreased odds of neurologically favorable survival compared with conventional bag-valve-mask ventilation.

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Out-of-hospital cardiac arrest (OHCA) is a major public health problem, occurring in 375 000 to 390 000 individuals in the United States each year.[1] The rate of survival after OHCA has increased with advances in care via initiatives such as the American Heart Association's 5-step Chain of Survival.[2] However, the rate is still low, with recent estimates reporting 8% to 10%.[3-5] Better survival has been associated with the improvement in early access to emergency medical care, early cardiopulmonary resuscitation (CPR), rapid defibrillation, and integrated post–cardiac arrest care.[6] Early advanced life support is often considered of benefit in that it provides intravenous drug therapy and advanced airway management.[6]

Although advanced airway management, such as endotracheal intubation or insertion of supraglottic airways, has long been the criterion standard for airway management of patients with OHCA,[7] recent studies have challenged the survival benefit of advanced airway management compared with conventional bag-valve-mask ventilation in this clinical

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setting.[8-14] However, large-scale studies evaluating the association between advanced airway management and patient-centered outcomes such as neurological status do not exist. Thus, whether prehospital advanced airway management by emergency medical service (EMS) personnel increases or decreases the rate of favorable neurological outcome among adults with OHCA remains to be determined.[15,16]

The purpose of the current study was to examine whether CPR with any type of out-of-hospital advanced airway management by EMS personnel, compared with CPR with conventional bag-valve-mask ventilation, would be associated with favorable neurological outcome in adult OHCA. In addition, we postulated that both advanced airway techniques (endotracheal intubation or use of supraglottic airways) would be similarly associated with favorable neurological outcome after OHCA.

METHODS

Study Design and Participants

The All-Japan Utstein Registry of the Fire and Disaster Management Agency (FDMA) is a prospective, nationwide, population-based registry system of OHCA in adults and children, with Utstein-style data collection.[17] This study enrolled all adults aged 18 years or older who had had OHCA and for whom resuscitation was attempted by EMS personnel with subsequent transport to medical institutions from January 1, 2005, to December 31, 2010. Patients were excluded from the analysis if out-of-hospital airway management or age was not documented. Cardiac arrest was defined as the end of cardiac mechanical activity determined by the absence of signs of circulation.[17-19] The ethics committees of Kinki University Faculty of Medicine and Massachusetts General Hospital approved the study with a waiver of informed consent.

Study Setting

The population of Japan was roughly 128 million in 2010, with approximately 107 million people aged 18 years or older.[20] The EMS system in Japan has been described previously.[21] Briefly, in Japan, municipal governments provided EMS through 802 fire stations with dispatch centers. All EMS personnel performed CPR according to the Japanese CPR guidelines, which are based on the American Heart Association and the International Liaison Committee on Resuscitation.[2,22,23] In most cases, an ambulance crew consisted of 3 EMS personnel, including at least 1 emergency lifesaving technician who had completed extensive training. These technicians were authorized to insert an intravenous line, to use semiautomated external defibrillators, and to lead CPR. In 1991, emergency lifesaving technicians were also permitted to use supraglottic airway devices (laryngeal mask airway, laryngeal tube, and esophageal-tracheal twin-lumen airway device) for patients with OHCA under medical control direction.[21] Beginning in 2004, endotracheal intubation could be performed by specially trained emergency lifesaving technicians who had completed an additional 62 hours of training sessions and performed 30 supervised successful intubations in operating rooms.[24]

Under medical control direction in the placement of an advanced airway device, the choice of either endotracheal intubation or supraglottic airway was at the discretion of each specially trained emergency lifesaving technician. Advanced airway management was performed, with efforts limited to a total of 2 attempts, after checking initial rhythm and using defibrillation when appropriate, along with chest compression and bag-valve-mask ventilation. Advanced airway device placement with successful ventilation was confirmed by an esophageal detection device and/or an end-tidal carbon dioxide monitor (quantitative or colorimetric).[24] The performance of CPR including prehospital advanced airway management was reviewed by local medical control committees.

Data Collection and Quality Control

Data were collected prospectively with an Utstein-style data form that included sex, age, etiology of arrest, bystander witness status, first documented cardiac rhythm, presence and type of CPR by bystander, administration of epinephrine by EMS personnel, and technique of airway management. A series of EMS times of call receipt, vehicle arrival at the scene, contact with patients, initiation of CPR, and hospital arrival were recorded based on the clock used by each EMS system. Outcome measures included return of spontaneous circulation before hospital arrival, 1-month survival, and neurological status 1 month after the event. To collect 1-month follow up data, the EMS personnel in charge of each patient with OHCA queried the medical control director at the hospital. Patient neurological status was determined by the treating physician; the EMS received a written response. If the patient was not at the hospital, the EMS personnel conducted a follow-up search.

Data forms were completed by the EMS personnel caring for the patients, and the data were integrated into the Utstein registry system on the FDMA database server. Forms were logically checked by the computer system and were confirmed by the FDMA. If the data form was incomplete, the FDMA returned it to the respective fire station and the data were reconfirmed.

Study End Points

The primary end point was favorable neurological outcome 1 month after cardiac arrest, defined a priori as Glasgow-Pittsburgh cerebral performance category 1 (good performance) or 2 (moderate disability).[17] The other categories—3 (severe cerebral disability), 4 (vegetative state), and 5 (death)—were regarded as unfavorable neurological outcomes.[17] Secondary outcome measures were return of spontaneous circulation before hospital arrival and 1-month survival.

Statistical Analysis

We compared outcomes between any advanced airway management and bag-valve-mask ventilation for all adult OHCA. Then, we compared outcomes between either advanced airway technique (endotracheal intubation or supraglottic airways) and bag-valve-mask ventilation. With the full cohort, 3 unconditional logistic regression models (unadjusted, adjusted for selected variables, and adjusted for all covariates) were fit using each of the 3 end points as a dependent variable. A set of potential confounders was chosen a priori based on biological plausibility and a priori knowledge. These selected variables included age, sex, cause of cardiac arrest, first documented rhythm, witnessed status, type of bystander CPR, use of a public access automated external defibrillator, epinephrine administration, and time intervals from receipt of call to CPR by EMS and from receipt of call to hospital arrival. All covariates included the selected variables above and year, lifesaving technician presence, physician presence in ambulance, defibrillation by EMS personnel, insertion of intravenous line, and prefecture.

Our data derive from 367 837 patients who underwent bag-valve-mask ventilation and 281 522 who underwent advanced airway management. On the assumption of an incidence of 3.0% favorable neurological outcomes in the bag-valve-mask group, the study has 90% power to detect a difference as small as 0.16% between the groups for the primary outcome with a 2-sided significance level of $P<.05$.

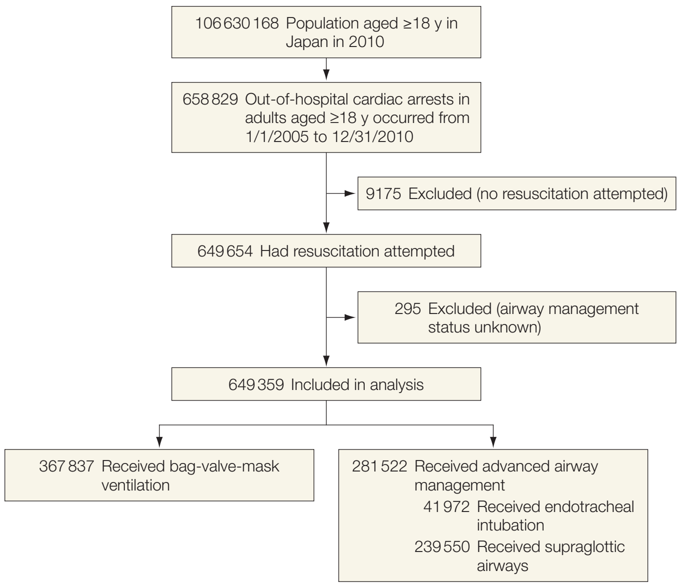
Prehospital advanced airway management was not randomly assigned in the study population; therefore, we used a propensity score approach to condition on potential selection bias and confounding. With a multivariable logistic regression model that did not take end points into account, we computed the propensity score, which represented the probability that a patient with cardiac arrest would undergo prehospital advanced airway management. Specifically, a full nonparsimonious model was fit with advanced airway management as the dependent variable, which included the variables in TABLE 1 in addition to dummy variables for the 47 prefectures in Japan as the independent variables. To maximize the efficacy of propensity score matching, missing values for categori-

Table 1. Out-of-Hospital Cardiac Arrest Population Baseline Characteristics According to Airway Management[a]

Characteristics	No. (%) Advanced Airway Management (n = 281 522)	No. (%) Bag-Valve-Mask Ventilation (n = 367 837)
Patients per year		
2005	44 503 (15.8)	55 988 (15.2)
2006	47 568 (16.9)	55 940 (15.2)
2007	46 398 (16.5)	57 404 (15.6)
2008	46 479 (16.5)	63 617 (17.3)
2009	47 244 (16.8)	64 924 (17.7)
2010	49 325 (17.5)	69 951 (19.0)
Age, mean (SD), y	73.2 (15.5)	72.7 (16.9)
Male sex	167 094 (59.4)	213 071 (57.9)
Etiology of cardiac arrest		
Cardiac	165 310 (58.7)	194 423 (52.9)
Noncardiac	116 212 (41.3)	173 414 (47.1)
External causes[b]	46 315 (16.5)	70 693 (19.2)
Respiratory disease	15 557 (5.5)	22 382 (6.1)
Cerebrovascular disease	13 960 (5.0)	17 522 (4.8)
Malignant tumor	7095 (2.5)	14 824 (4.0)
Other	33 285 (11.8)	47 993 (13.0)
Initial cardiac rhythm		
Ventricular fibrillation or tachycardia	21 867 (7.8)	26 366 (7.2)
Pulseless electrical activity/asystole	259 655 (92.2)	341 471 (92.8)
Bystander witness status[c]		
No witness	159 014 (58.1)	208 689 (58.1)
Layperson	100 647 (36.8)	111 992 (31.2)
Health care practitioner	14 227 (5.2)	38 666 (10.8)
CPR by bystander		
No bystander CPR	160 622 (58.0)	234 811 (64.7)
Compression-only CPR	76 562 (27.7)	85 971 (23.7)
Conventional CPR	39 567 (14.3)	42 396 (11.7)
Use of public-access AED by bystander	1299 (0.5)	1998 (0.6)
CPR by emergency responder		
Emergency lifesaving technician present in ambulance	279 954 (99.5)	333 151 (90.6)
Physician present in ambulance	6754 (2.4)	10 269 (2.8)
Defibrillation by emergency responder	33 016 (11.8)	36 937 (10.1)
Epinephrine administered	29 515 (10.6)	10 709 (2.9)
Insertion of intravenous line	102 586 (36.5)	38 132 (10.4)
Time from call to CPR by emergency responder, median (IQR), min	8 (7-11)	9 (7-12)
Time from call to hospital arrival, median (IQR), min	32 (26-39)	28 (23-36)
Time from CPR by emergency responder to ROSC, median (IQR), min[d]	14 (8-20)	6 (3-12)

Abbreviations: AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; IQR, interquartile range; ROSC, return of spontaneous circulation.
[a] Data are expressed as No. (%) of population unless otherwise indicated. All baseline characteristic comparisons between the 2 groups were statistically significant at $P<.001$.
[b] Defined as cardiac arrest due to trauma, hanging, drowning, intoxication, or asphyxia.
[c] Percentages do not sum to 100 because of missing data.
[d] Calculated for cases with ROSC.

Figure 1. Study Participant Selection



cal variables included in the propensity score model (bystander witness status, bystander CPR, use of a public access automated external defibrillator, use of epinephrine, defibrillation by EMS, and insertion of intravenous line) were dummy coded using the missing indicator method (eTable 1; available at http://www.jama.com). Using the match algorithm by Parsons,[25] based on propensity score, a subgroup of patients with cardiac arrest requiring advanced airway management were matched with unique control patients who underwent bag-valve-mask ventilation. Then, 3 conditional logistic regression models (unadjusted, adjusted for selected variables, and adjusted for all covariates) were fit with each of the 3 end points as a dependent variable.

All statistical analyses were performed with SAS statistical software, version 9.3 (SAS Institute Inc). All statistical tests were 2-tailed. The chosen type 1 error rate was $P<.05$, except when testing the subgroup of patients with endotracheal intubation or supraglottic airways for which a Bonferroni adjustment for multiplicity was used ($P<.025$).

RESULTS

A total of 658 829 adult patients with OHCA were documented. Among 649 654 resuscitation attempts, 295 arrests with unknown airway management status were excluded (FIGURE 1). Of the remaining 649 359 patients, 367 837 (56.7%; 95% CI, 56.5%-56.8%) underwent bag-valve-mask and 281 522 (43.4%; 95% CI, 43.2%-43.5%) underwent advanced airway management, including 41 972 (6.5%; 95% CI, 6.4%-6.5%) with endotracheal intubation and 239 550 (36.9%; 95% CI, 36.8%-37.0%) with supraglottic airways.

Table 1 shows the demographic characteristics for adult OHCA by type of airway management. The mean age of all patients was 73 years; the majority were male. TABLE 2 summarizes survival outcomes by airway management among all patients. Overall, rates of return of spontaneous circulation, 1-month survival, and neurologically favorable survival were 6.5% (95% CI, 6.5%-6.6%), 4.7% (95% CI, 4.7%-4.8%), and 2.2% (95% CI, 2.1%-2.2%), respectively. The rates of neurologically favorable survival were 1.0% (95% CI, 0.9%-1.1%) in the endotracheal intubation group, 1.1% (95% CI, 1.1%-1.2%) in the supraglottic airway group, and 2.9% (95% CI, 2.9%-3.0%) in the bag-valve-mask ventilation group. The unadjusted model using the full cohort demonstrated significant negative associations between any advanced airway management and the 3 end-point measures ($P<.001$ for all) (Table 2). Similarly, in the adjusted model using the selected variables and all variables, both advanced airway techniques (endotracheal intubation and supraglottic airways) were independent negative predictor of all 3 outcomes ($P<.001$for all; Table 2).

To assess the robustness of the results, we performed a series of sensitivity analyses (TABLE 3). First, in an analysis of patients lost to follow-up, when assuming that all missing patients in the bag-valve-mask group (n=444) had an unfavorable neurological outcome and all missing patients in the advanced airway group (n=366) had a favorable outcome, advanced airway management was still a significant negative predictor of favorable neurological outcome after adjusting for selected variables (adjusted odds ratio [OR], 0.43; 95% CI, 0.42-0.45). When adjusting for achievement of return of spontaneous circulation in addition to the selected variables, the adjusted association of endotracheal intubation and supraglottic airways with poor neurological outcome persisted (OR, 0.51 [95% CI, 0.45-0.56] and OR, 0.52 [95% CI, 0.49-0.54], respectively) (Table 3). Similarly, the adjusted association persisted with stratification by achievement of return of spontaneous circulation, etiology of cardiac arrest, first documented rhythm, and type of witness status (Table 3).

Demographic characteristics were similar between the propensity-matched groups (TABLE 4). FIGURE 2 and eTable 2 summarize survival outcomes by airway management among propensity-matched patients. The unadjusted model showed significant negative associations between advanced airway management, regardless of its technique, and the 3 end-point measures ($P < .001$ for all). In the multivariable models using selected and all variables, significant negative associations were detected between any type of advanced airway management and the 3 outcome measures (Figure 2). In particular, the adjusted OR for neurologically favorable survival was 0.45 (95% CI, 0.37-0.55; $P < .001$) for endotracheal intubation and 0.36 (95% CI, 0.33-0.39; $P < .001$) for supraglottic airways compared with bag-valve-mask ventilation after controlling for the selected variables.

COMMENT

In this nationwide population-based cohort study of patients with OHCA, we found that CPR with advanced airway management was a significant predictor of poor neurological outcome compared with conventional bag-valve-mask ventilation. Unlike an earlier study that was underpowered to identify this clinically important association,[11] our study was sufficiently large to clearly demonstrate the negative association between advanced airway management and neurologically favorable survival after cardiac arrest. Furthermore, both endotracheal intubation and supraglottic airways were similarly associated with a decreased chance of favorable neurological outcome. The observed associations were large and persisted across different analytic assumptions.

Our clinical data are consistent with findings from several studies in trauma and pediatric patients.[7,8] These studies have suggested that prehospital endotracheal intubation may lead to a decreased rate of favorable neurological outcome, and only a few studies have demonstrated benefit from endotracheal intubation.[7] Additionally, several studies of OHCA have demonstrated the association between endotracheal intubation and decreased survival to hospital discharge.[9,10,13] An important unanswered question regards the mechanism connecting endotracheal intubation with poor outcomes. It has been well documented that prehospital intubation is a complex psychomotor task and that EMS personnel have difficulty gaining and maintaining competency in this skill.[7] Endotracheal intubation by unskilled practitioners can produce ad-

Table 2. Unconditional Logistic Regression Analyses for Outcomes Comparing Prehospital Advanced Airway Management vs Bag-Valve-Mask Ventilation

			Advanced Airway Management					
			Overall		Endotracheal Intubation		Supraglottic Airway	
Model	Total No. of Patients	Bag-Valve-Mask Ventilation, No. (%)	No. (%)	OR (95% CI) vs Bag-Valve-Mask[a]	No. (%)	OR (95% CI) vs Bag-Valve-Mask[a]	No. (%)	OR (95% CI) vs Bag-Valve-Mask[a]
Total	649 359	367 837 (56.7)	281 522 (43.4)		41 972 (6.5)		239 550 (36.9)	
Return of spontaneous circulation								
Unadjusted	649 326	25 904 (7.0)	16 299 (5.8)	0.81 (0.79-0.83)	3514 (8.4)	1.21 (1.16-1.25)	12 785 (5.3)	0.74 (0.73-0.76)
Adjusted for selected variables[b]				0.67 (0.66-0.69)		0.86 (0.82-0.89)		0.64 (0.62-0.65)
Adjusted for all variables[c]				0.57 (0.56-0.58)		0.73 (0.70-0.77)		0.54 (0.52-0.55)
One-month survival								
Unadjusted	649 350	19 643 (5.3)	10 933 (3.9)	0.72 (0.70-0.73)	1757 (4.2)	0.77 (0.74-0.81)	9176 (3.8)	0.71 (0.69-0.72)
Adjusted for selected variables[b]				0.73 (0.71-0.75)		0.83 (0.79-0.88)		0.72 (0.70-0.74)
Adjusted for all variables[c]				0.62 (0.60-0.64)		0.69 (0.65-0.73)		0.61 (0.59-0.63)
Neurologically favorable survival								
Unadjusted	648 549	10 759 (2.9)	3156 (1.1)	0.38 (0.36-0.39)	432 (1.0)	0.35 (0.31-0.38)	2724 (1.1)	0.38 (0.37-0.40)
Adjusted for selected variables[b]				0.38 (0.37-0.40)		0.41 (0.37-0.45)		0.38 (0.36-0.40)
Adjusted for all variables[c]				0.32 (0.30-0.33)		0.32 (0.29-0.36)		0.32 (0.30-0.33)

Abbreviation: OR, odds ratio.
[a] $P < .001$ for all.
[b] Selected variables are a predefined set of potential confounders including age, sex, cause of cardiac arrest, first documented rhythm, bystander witness, type of cardiopulmonary resuscitation (CPR) initiated by bystander, use of a public access automated external defibrillator by bystander, epinephrine administration, time from receipt of call to CPR by emergency medical service, and time from receipt of call to hospital arrival.
[c] Adjustment for all variables included in Table 1 and dummy variables for the 47 prefectures in Japan.

verse events, such as unrecognized esophageal intubation, tube dislodgement, iatrogenic hypoxemia, and bradycardia.[26] Furthermore, prehospital intubation may influence patient outcome by affecting the execution of simultaneous basic life support procedures, resulting in ineffective chest compressions with significant interruptions.[7]

Most studies of prehospital airway management using supraglottic airways have focused on process measures, such as success rates and speed of placement. Most of these found higher success rates and faster placement for the supraglottic airways.[27-29] From a physiological perspective, one might expect this to translate into better outcomes because of fewer interruptions of chest compressions. However, we observed that not only endotracheal intubation but also supraglottic airways were independently associated with a lower rate of neurologically favorable survival. Our finding is consistent with a recent study that failed to demonstrate a survival advantage with supraglottic airways in patients with OHCA.[12] Assuming the validity of our study, a more secure airway, regardless of its technique, would be detrimental. Previous studies have shown that inadvertent hyperventilation after advanced airway management can cause increased intrathoracic pressure, leading to decreased coronary and cerebral perfusion pressure among intubated patients with OHCA.[30,31] The literature has also reported that hyperoxia among patients following resuscitation from cardiac arrest was associated with increased mortality.[32,33] These unanticipated physiologic effects may offset the potential benefits of proper advanced airway management.

High-quality prospective clinical trials of prehospital airway management would be instrumental in revealing causality between airway manage-

Table 3. Sensitivity and Stratified Analyses of Multivariable Associations With Neurologically Favorable Survival and Airway Management in the Total Patient Population[a]

Model	Total No. of Patients	Bag-Valve-Mask Ventilation, No. (%)	Advanced Airway Management: Overall, No. (%)	Overall, OR (95% CI) vs Bag-Valve-Mask[b]	Endotracheal Intubation, No. (%)	Endotracheal Intubation, OR (95% CI) vs Bag-Valve-Mask[b]	Supraglottic Airway, No. (%)	Supraglottic Airway, OR (95% CI) vs Bag-Valve-Mask[b]
Sensitivity analysis								
Including loss to follow-up	649 359	10 759 (2.9)	3522 (1.3)	0.43 (0.42-0.45)	457 (1.1)	0.44 (0.39-0.48)	3065 (1.3)	0.43 (0.41-0.45)
Adjusted for ROSC[c]	648 517	10 759 (2.9)	3156 (1.1)	0.51 (0.45-0.56)	432 (1.0)	0.51 (0.45-0.56)	2724 (1.1)	0.52 (0.49-0.54)
Stratification by achievement of ROSC prior to hospital arrival								
ROSC[d]	42 203	8660 (33.5)	2184 (13.4)	0.61 (0.57-0.65)	297 (8.5)	0.65 (0.57-0.75)	1887 (14.5)	0.60 (0.56-0.64)
No ROSC	607 123	2098 (0.6)	969 (0.4)	0.65 (0.60-0.71)	134 (0.4)	0.71 (0.59-0.85)	835 (0.4)	0.65 (0.59-0.70)
Stratification by etiology								
Cardiac origin	359 733	8199 (4.2)	2410 (1.5)	0.36 (0.34-0.38)	293 (1.3)	0.36 (0.32-0.41)	2117 (1.5)	0.36 (0.34-0.38)
Noncardiac origin	289 626	2560 (1.5)	746 (0.6)	0.46 (0.42-0.50)	139 (0.7)	0.51 (0.43-0.61)	607 (0.6)	0.45 (0.41-0.49)
Stratification by initial rhythm								
Ventricular fibrillation or ventricular tachycardia	48 233	5296 (20.1)	1697 (7.8)	0.36 (0.34-0.39)	189 (6.6)	0.34 (0.29-0.40)	1508 (8.0)	0.37 (0.34-0.39)
Pulseless electrical activity/asystole	601 126	5463 (1.6)	1459 (0.6)	0.40 (0.38-0.43)	243 (0.6)	0.47 (0.42-0.54)	1216 (0.6)	0.39 (0.37-0.42)
Stratification by witness status								
Not witnessed	367 363	1635 (0.8)	665 (0.4)	0.49 (0.44-0.53)	80 (0.4)	0.47 (0.37-0.59)	585 (0.4)	0.49 (0.44-0.54)
Witnessed by layperson	212 639	5690 (5.1)	2068 (2.0)	0.39 (0.37-0.41)	303 (1.8)	0.43 (0.38-0.49)	1765 (2.1)	0.38 (0.36-0.43)
Witnessed by EMS	52 893	3383 (8.8)	383 (2.7)	0.29 (0.26-0.32)	43 (2.3)	0.27 (0.20-0.37)	340 (2.8)	0.29 (0.26-0.33)

Abbreviations: EMS, emergency medical service; OR, odds ratio; ROSC, return of spontaneous circulation.

[a] Unconditional logistic regression models adjusted for selected variables including age, sex, cause of cardiac arrest, first documented rhythm, bystander witness, type of cardiopulmonary resuscitation (CPR) initiated by bystander, use of a public access automated external defibrillator by bystander, epinephrine administration, time from receipt of call to CPR by EMS, and time from receipt of call to hospital arrival.

[b] $P < .001$ for all.

[c] Adjusted for achievement of ROSC in addition to the above selected variables.

[d] Adjusted for time from cardiopulmonary resuscitation by EMS to ROSC in addition to the above selected variables.

ment and outcomes. However, such trials are logistically and methodologically difficult in this clinical setting.[26,34] Additionally, as trials are often designed to address specific questions in select groups, the characteristics of trial populations may differ significantly from those of the general population. As an alternative, our prospective nationwide cohort data reflect the effectiveness of prehospital airway management in the natural setting of a "real" population and current clinical practice, therefore enhancing the potential generalizability of the findings. In addition, multiple studies arrived at similar conclusions despite differing populations, disease groups, and designs.[7-10,12,13] There are plausible mechanisms to support this conclusion. Thus, our data lend significant support to the concept that prehospital intubation and its alternatives are less effective, or even harmful, than was previously believed.

Should clinicians avoid advanced airway management during CPR based on the best available observational evidence? Although one option would be to remove advanced airway management from the skill set of all out-of-hospital rescuers, that approach would disregard situations in which advanced airway management would be expected to be efficacious, especially for long-distance transfers and respiratory failure not yet with cardiac arrest.[35] Future research will need to identify whether there are subsets of patients for whom prehospital advanced airway management is beneficial. In addition, as observational studies cannot establish causal relationships in the way that randomized trials can, a rigorously conducted and adequately powered clinical trial evaluating this criterion standard in patients with OHCA now seems timely and necessary. While awaiting results of such a trial, we believe that decision makers for communities and national organizations should rethink the approach to prehospital airway management and need to invest more resources in optimizing the first 3 links in the chain of survival for the promotion of better outcomes among patients with OHCA.

This study has several limitations. First, as with any observational study, the negative association between any type of out-of-hospital advanced airway management and favorable neurological outcome does not necessarily prove causality and might be confounded by unmeasured factors. Despite a rigorous adjustment for confounding factors with a propensity score–matched analysis, there are other variables that may have contributed for which our study was unable to control or that were not collected a priori. Examples of potential confounding variables include rural or urban distinction, location of cardiac arrest, time interval from cardiac arrest onset to CPR among unwitnessed cardiac arrests, individual rescuer training levels, hospital-level variables, and postresuscitation care such as induced hypothermia therapy. Additionally, one might surmise that patients

Table 4. Baseline Characteristics of Propensity-Matched Patients With Out-of-Hospital Cardiac Arrest According to Airway Management

Characteristics	No. (%)[a] Advanced Airway Management (n = 178 614)	Bag-Valve-Mask Ventilation (n = 178 614)
Patients per year		
2005	27 058 (15.1)	27 795 (15.6)
2006	28 002 (15.7)	28 367 (15.9)
2007	28 448 (15.9)	28 494 (16.0)
2008	30 771 (17.2)	30 284 (17.0)
2009	31 294 (17.5)	30 784 (17.2)
2010	33 041 (18.5)	32 892 (18.4)
Age, mean (SD), y	72.9 (15.8)	72.9 (16.8)
Male sex	104 427 (58.5)	104 575 (58.5)
Etiology of cardiac arrest		
Cardiac	99 383 (55.6)	99 586 (55.8)
Noncardiac	79 231 (44.4)	79 028 (44.2)
Initial cardiac rhythm		
Ventricular fibrillation or tachycardia	13 519 (7.6)	13 557 (7.6)
Pulseless electrical activity/asystole	165 095 (92.4)	165 057 (92.4)
Bystander witness status[b]		
No witness	102 437 (57.4)	102 435 (57.3)
Layperson	60 143 (33.7)	60 581 (33.9)
Health care practitioner	11 704 (6.6)	11 149 (6.2)
CPR by bystander[b]		
No bystander CPR	106 591 (59.7)	105 753 (59.2)
Compression-only CPR	46 814 (26.2)	47 290 (26.5)
Conventional CPR	22 850 (12.8)	23 224 (13.0)
Use of public access AED by bystander	921 (0.5)	924 (0.5)
CPR by emergency responder		
Emergency lifesaving technician present in ambulance	177 076 (99.1)	178 316 (99.3)
Physician present in ambulance	4772 (2.7)	4581 (2.6)
Defibrillation by emergency responder	19 509 (10.9)	19 584 (11.0)
Epinephrine administered	10 159 (5.7)	9744 (5.5)
Insertion of intravenous line	37 602 (21.1)	36 051 (20.2)
Time from call to CPR by emergency responder, median (IQR), min	8 (7-11)	8 (7-11)
Time from call to hospital arrival, median (IQR), min	31 (25-38)	29 (23-37)

Abbreviations: AED, automated external defibrillator; CPR, cardiopulmonary resuscitation; IQR, interquartile range.
[a] Data are expressed as No. (%) of population unless otherwise indicated.
[b] Percentages do not sum to 100 because of missing data.

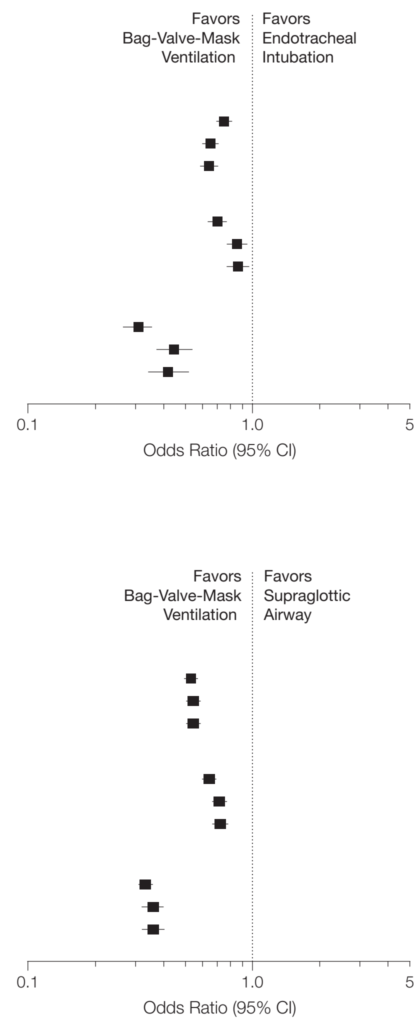
with return of spontaneous circulation prior to any airway management would have subsequently received bag-valve-mask ventilation rather than advanced airway management. These patients may have had neurologically favorable survival more frequently because of early return of spontaneous circulation rather than choice of airway management. However, the subgroup analysis limited to patients who achieved return of spontaneous circulation prior to hospital arrival demonstrated that advanced airway management, regardless of its type, still remained a significant negative predictor for the outcome even after adjusting for time interval from CPR to return of spontaneous circulation. Similarly, in the subgroup analysis of patients who did not achieve return of spontaneous circulation, the adjusted association of advanced airway management with poor neurological outcome persisted. Both suggest that this choice of airway management is the important variable.

Our study is also limited by the absence of information regarding the process of intubation. Indeed, up to 20% of out-of-hospital tracheal intubation efforts may fail.[36] However, we defined advanced airway management as suc-

Figure 2. Results of Conditional Logistic Regression Models Using One of the End Points as a Dependent Variable With Propensity-Matched Patients

A Endotracheal intubation vs bag-valve-mask ventilation

Model	Total No. of Patients	No. (%) Endotracheal Intubation	No. (%) Bag-Valve-Mask Ventilation	Odds Ratio (95% CI)[a]
Total		26 013 (7.3)	178 614 (50.0)	
Return of spontaneous circulation				
Unadjusted	357 228	1734 (6.7)	14 824 (8.3)	0.76 (0.71-0.81)
Adjusted for selected variables[b]				0.66 (0.61-0.72)
Adjusted for all variables[c]				0.64 (0.58-0.70)
1-month survival				
Unadjusted	357 228	1069 (4.1)	10 373 (5.8)	0.70 (0.65-0.76)
Adjusted for selected variables[b]				0.87 (0.79-0.97)
Adjusted for all variables[c]				0.88 (0.79-0.98)
Neurologically favorable survival				
Unadjusted	357 228	257 (1.0)	5799 (3.2)	0.31 (0.27-0.35)
Adjusted for selected variables[b]				0.45 (0.37-0.55)
Adjusted for all variables[c]				0.42 (0.34-0.53)



B Supraglottic airway vs bag-valve-mask ventilation

Model	Total No. of Patients	No. (%) Supraglottic Airway	No. (%) Bag-Valve-Mask Ventilation	Odds Ratio (95% CI)[a]
Total		152 601 (42.7)	178 614 (50.0)	
Return of spontaneous circulation				
Unadjusted	357 228	6933 (4.5)	14 824 (8.3)	0.53 (0.51-0.54)
Adjusted for selected variables[b]				0.54 (0.52-0.56)
Adjusted for all variables[c]				0.54 (0.52-0.56)
1-month survival				
Unadjusted	357 228	5718 (3.8)	10 373 (5.8)	0.63 (0.61-0.65)
Adjusted for selected variables[b]				0.71 (0.68-0.74)
Adjusted for all variables[c]				0.72 (0.68-0.75)
Neurologically favorable survival				
Unadjusted	357 228	1697 (1.1)	5799 (3.2)	0.33 (0.32-0.35)
Adjusted for selected variables[b]				0.36 (0.33-0.39)
Adjusted for all variables[c]				0.36 (0.33-0.40)

Full models for the primary outcome analysis are included in eTable 2.

[a] For all odds ratios, $P < .001$.

[b] Selected variables are a predefined set of potential confounders including age, sex, cause of cardiac arrest, first documented rhythm, bystander witness, type of cardiopulmonary resuscitation (CPR) initiated by a bystander, use of public access automated external defibrillator by bystander, epinephrine administration, time from receipt of call to CPR by emergency medical service, and time from receipt of call to hospital arrival.

[c] All variables included all covariates in Table 1 and variables for 47 prefectures in Japan.

cessful endotracheal intubation or supraglottic airway placement only. Thus, in our study, failed advanced airway management cases reverted to and were classified as bag-valve-mask ventilation cases. This would have biased our conclusions toward the null.

Another limitation is that our analysis of a nationwide population-based cohort describes that in Japan only. Similar studies with data from other countries may result in different findings. In particular, one might hypothesize that training of airway management for Japanese EMS personnel is relatively suboptimal, resulting in poor outcomes. However, the certification process for EMS personnel credentialed to perform endotracheal intubation in Japan is stricter than that in other countries. Indeed, the national paramedic curriculum in the United States requires students to perform 5 successful endotracheal intubations to graduate; 25 successful intubations are required in the United Kingdom and 30 are required in Japan.[37-39] Furthermore, existing literature suggests that intubation proficiency is attained by EMS personnel after 15 to 20 successful endotracheal intubations (predicted intubation success threshold of 90%).[40] This would serve not to reduce the potential generalizability of our inference to other settings.

Finally, as with all epidemiological studies, data integrity, validity, and ascertainment bias are potential limitations. The use of uniform data collection on the basis of Utstein-style guidelines for reporting cardiac arrest, large sample size, and a population-based design were intended to minimize these potential sources of biases.

This large, nationwide, population-based cohort study showed that CPR with prehospital advanced airway management, whether endotracheal intubation or supraglottic airways, was independently associated with a decreased likelihood of favorable neurological outcome compared with conventional bag-valve-mask ventilation among adults with OHCA. Our observations contradict the assumption that aggressive airway intervention is associated with improved outcomes and provide an opportunity to reconsider the approach to prehospital airway management in this population.

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Study concept and design: Hasegawa, Brown.
Acquisition of data: Hasegawa, Hiraide.
Analysis and interpretation of data: Hasegawa, Chang, Brown.
Drafting of the manuscript: Hasegawa.
Critical revision of the manuscript for important intellectual content: Hasegawa, Hiraide, Chang, Brown.
Statistical analysis: Hasegawa, Chang.
Obtaining funding: Hiraide.
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Study supervision: Hasegawa, Hiraide, Brown.
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