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Appendix

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Supplemental Files

Supplemental File 1

Table S1. Cardiovascular Events in Each Group

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Original article

Impact of diabetes mellitus on outcomes in Japanese patients undergoing coronary artery bypass grafting[☆]

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Renal insufficiency

Summary
Background and purpose: There have been no large-scale studies on the impact of diabetes mellitus (DM) on outcomes in Japanese patients undergoing coronary artery bypass grafting (CABG).
Methods and subjects: A multi-institutional retrospective cohort study was conducted in 14 Japanese centers. All adult patients who underwent isolated CABG from 2007 to 2008 were included ($n = 1522$, mean age: 68.5 years). The definitions of DM were all patients admitted with diagnosis of DM and preoperative glycated hemoglobin (Hb) A1c $\geq 6.5\%$. Univariate and multivariate analyses were performed to identify the risk of morbidity and mortality.
Results: There were 849 DM and 572 non-DM patients. Preoperative mean HbA1c were 7.1% in the DM group and 5.7% in the non-DM group ($p < 0.0001$). Preoperative, intraoperative, and 3-day average postoperative blood glucose (BG) were 146 mg/dl, 172 mg/dl, and 168 mg/dl in the DM group, and 103 mg/dl, 140 mg/dl, and 136 mg/dl in the non-DM group (all $p < 0.0001$). Although there were no significant differences in postoperative cardiovascular events, the incidence of infection was significantly higher in the DM group than in the non-DM group (9.2% vs 6.1%, $p = 0.036$) on the univariate analysis. The all-cause death was also relatively higher in the DM group than in the non-DM group (2.1% vs 1.1%, $p = 0.12$), and this was likely related to infection.
Conclusion: DM patients had worse perioperative BG control, higher incidence of infection, and higher mortality than non-DM patients. These results indicate that perioperative BG control guidelines should be standardized to obtain better surgical outcomes in Japanese DM patients.

Introduction

The prevalence of diabetes mellitus (DM) has increased dramatically in Western countries over the past several decades, leading in turn to increased mortality due to cardiovascular events [1]. This trend is also apparent in Asian countries, especially in Japan, where the number of DM patients has increased from 6.9 million to 8.9 million in the past decade (a 29% increase) [2]. The most important life-threatening complication in DM patients is obviously coronary artery disease [3]. There has been debate regarding the optimal treatment for DM patients; some physicians favor percutaneous catheter intervention (PCI), while others favor coronary artery bypass grafting (CABG). Some studies have shown that CABG yields better long-term outcomes in DM patients with multivessel disease [4,5]. However, it is well known that patients with DM who undergo CABG have worse early and late outcomes than CABG patients without DM [6,7]. Also, it has been shown that intraoperative and postoperative blood glucose (BG) control has a significant effect on complications such as infection and mortality [8—10]. However, there have been no large-scale studies on Japanese DM patients undergoing CABG. To better understand the impact of DM on coronary artery surgery and to establish the optimal BG control method during cardiac surgery, we organized a multicenter/multidisciplinary research group, which we called the JMAP study group (Japanese Study to Explore the Impact of Diabetes on Cardiac Surgery for Optimal Glycemic Control Protocol). Herein, we carried out a retrospective cohort study to identify the impact of DM and BG control on surgical outcomes in Japanese patients undergoing CABG.

Materials and methods

From 2007 to 2008, a total of 1522 patients underwent isolated CABG in 14 cardiac surgery centers including 10 university hospitals (Appendix I) in Japan. Patients who underwent redo CABG were included, but patients who underwent concomitant procedures such as valvular procedures, aneurysm repair, arrhythmia surgery, repair of ventricular septal perforation, and surgical ventricular restoration procedures were excluded from this study. The number of the cases enrolled in each hospital varied from 8 to 365, also the number of the operating surgeons ranged from one to three. All the patient characteristics and operative data were extracted from the prospective national database (the Japan Adult Cardiovascular Surgery Database: JACVSD), which is similar to the Society of Thoracic Surgeons (STS) national database in North America. Other study-specific data like preoperative glycated hemoglobin (Hb)A1c and perioperative BG control, as well as other blood laboratory data and postoperative complications including cardiovascular events and individual infections, which are not included in the JACVSD, were obtained from medical records at each study site. These two sets of data were merged, then blinded, and sent to a data center (the EBM Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan).

Demographic variables are listed in Appendix II. Of note, the Japanese Diabetes Society (JDS) value of HbA1c (%) is converted into the National Glycohemoglobin Standardization Program (NGSP) equivalent value (%) calculated by the following formula according to the JDS guidelines [11]:

$$\text{HbA1c}\quad(\text{NGSP})\,(\%) = \text{HbA1c}\quad(\text{JDS})\,(\%) + 0.4\,(\%)$$

Postoperative variables were acute myocardial infarction (MI), cerebrovascular events, acute renal failure, and other cardiovascular events (including cardiac tamponade, ventricular tachycardia or fibrillation, and complications after PCI). Postoperative infection was categorized into deep sternal wound infection (anterior mediastinitis), superficial sternal wound infection, graft harvesting site infection, blood stream infection, urinary tract infection, and pneumonia. Details of the definitions of the clinical events are summarized in Appendix III. Hospital death included all-cause death within 30 days of operation or during initial hospitalization. All the aforementioned clinical events were evaluated at the participating centers, and then assessed by the independent clinical events evaluation committee (Appendix IV) if necessary. The primary composite endpoint was defined as a composite of acute MI, cerebrovascular accidents, other cardiovascular events, all infections and their related deaths. Although cardio-cerebrovascular events were thought to be important for DM patients, this prespecified primary composite endpoint was not related to DM. Thus, we added a new composite endpoint (the additional composite endpoint), which consisted of all infections, acute renal failure, and all-cause deaths, and conducted a post hoc analysis.

DM patients were defined as those patients who were admitted to the participating hospitals with a diagnosis of DM. Patients without a previous diagnosis of DM who had preoperative HbA1c $\geq$ 6.5% (NGSP) were also included [12]. The intraoperative BG was an average of 3—4 BG measurements taken during surgery. In the intensive care unit, the frequency of BG measurement was similar among the participating hospitals: BG was measured every 2—4 h in patients with intravenous continuous insulin infusion, and at least 4 times in non-diabetic patients without insulin. The postoperative 3-day BG average was a composite average of the daily mean BG levels (BG was measured up to 12 times per day following surgery) from the day of the surgery to postoperative day 3.

Perioperative BG control methods varied from hospital to hospital, however, in all the participating institutions, it was standard practice to treat hyperglycemia with continuous insulin infusion whenever BG exceeded 200 mg/dl. Preoperative renal insufficiency was defined as an increased serum creatinine level equal to or more than 2.0 mg/dl. The internal thoracic arteries were harvested by means of skeletonized fashion using the Harmonic Scalpel (Ethicon, West Somerville, NJ, USA) in most of the participating centers. In terms of intraoperative steroid use, a large amount of steroid (methylprednisolone 500—1000 mg) was primed in a cardiopulmonary bypass circuit in some centers for on-pump CABG cases. Also, some surgeons and anesthesiologists preferred to give a moderate amount of intravenous steroid (methylprednisolone 125—500 mg) immediately after starting off-pump CABG cases to prevent systemic inflammatory responses.

Statistical analyses

Baseline characteristics of the DM and the non-DM groups are described as mean ± standard deviation for continuous variables and proportions for categorical variables. *p*-Values were calculated by the *t*-test and the chi-squared test. We compared the proportions of primary and additional composite endpoints and their components between the DM and the non-DM groups. Risk ratios and associated 95% confidence intervals were calculated.

Logistic regression analyses were conducted to estimate the magnitude of the effect of DM on the additional composite endpoint, all infections, and all-cause deaths adjusted by age (in 10-year increments), gender, body mass index, congestive heart failure, renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, left ventricular ejection fraction < 50%, operative status (elective vs urgent or emergency), bilateral internal thoracic artery use, and intraoperative steroid use. Of note, these factors were prefixed before the statistical analyses. Odds ratios and their associated 95% confidence intervals were calculated. All analyses were performed with JMP 8.0 statistics software (SAS Institute Inc., Cary, NC, USA). The two-sided alpha level was set to 5%.

This study was approved by the Internal Review Board at all the participating hospitals and the Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine. All the patients and their families gave written consent at the time of operation for participation in the JACVSD.

Results

A total of 1522 enrolled patients were classified into two groups: the DM group (n = 849) and the non-DM group (n = 572). Because there were no preoperative HbA1c data for 101 patients without a previous diagnosis of DM, these patients were excluded from this study. The preoperative management of BG in the DM group included subcutaneous insulin injection in 254 patients (29.9%), oral medications in 342 (40.3%), and diet regulation in 233 (27.4%). Patients' baseline characteristics are shown in Table 1. There were no differences in terms of age, gender, and body mass index (BMI). However, depressed left ventricular systolic function (ejection fraction < 50%), renal insufficiency, and peripheral artery disease were significantly higher in the DM group than in the non-DM group. On the other hand, chronic obstructive pulmonary disease was less common in the DM group. There was no difference in terms of usage of bilateral internal thoracic artery, however intraoperative administration of intravenous steroids was more common in the non-DM group. There were no differences in operative status. Off-pump technique was used frequently in both groups (about 70% of patients in each group).

Preoperative mean HbA1c were 7.1% in the DM group and 5.7% in the non-DM group (p < 0.0001). Also, preoperative fasting, intraoperative, and 3-day average postoperative BG were 146 mg/dl, 172 mg/dl, and 168 mg/dl in the DM group, and 103 mg/dl, 140 mg/dl, and 136 mg/dl in the non-DM group, respectively. At all measurement points, DM patients had significantly higher BG levels (p < 0.0001). In terms of postoperative BG control, 71% of the patients in the DM group were treated with continuous insulin infusion whereas only 22% of the patients in the non-DM group were treated with continuous insulin infusion. As shown in Table 2, the all-cause deaths were 2.1% (n = 18) in the DM group and 1.1% (n = 6) in non-DM group (p = 0.124). There was no significant difference in the primary composite endpoint, however, the additional composite endpoint was significantly higher in the DM group. In terms of complications, although there were no significant differences in the incidence of postoperative cardiovascular events and cerebrovascular accidents, the incidence of overall infection was significantly higher in the DM group than in the non-DM group (9.2% vs 6.1%,

Table 1 Patients' baseline characteristics.

Variables	DM group ($n = 849$)	Non-DM group ($n = 572$)	p-Value
Mean age (SD)	68.6 (8.4)	68.0 (10.1)	0.282
Age ≥ 75	208 (24.5%)	162 (28.3%)	0.107
Male gender	649 (76.4%)	451 (78.9%)	0.288
Preoperative HbA1c (SD)	7.1% (1.2)	5.7% (0.4)	<0.0001
Mean body mass index (SD)	23.7 (3.3)	23.4 (3.1)	0.094
Preoperative steroid use	18 (2.1%)	8 (1.4%)	0.320
Congestive heart failure	131 (15.5%)	98 (17.1%)	0.397
Renal insufficiency	117 (13.8%)	45 (7.9%)	0.001
Chronic obstructive pulmonary disease	57 (6.7%)	64 (11.2%)	0.003
Peripheral artery disease	193 (22.7%)	101 (17.7%)	0.021
Left ventricular ejection fraction < 50%	212 (26.6%)	115 (20.5%)	0.010
Operative status			
Elective	732 (86.2%)	484 (84.6%)	0.154
Urgent	76 (9.0%)	67 (11.7%)	
Emergency	41 (4.8%)	21 (3.7%)	
Bilateral internal thoracic artery use	400 (47.1%)	285 (49.8%)	0.316
Intraoperative steroid use	246 (29.0%)	200 (35.0%)	0.017
On-pump or off-pump			
On-pump	214 (25.2%)	154 (26.9%)	0.754
On-pump beating	43 (5.1%)	27 (4.7%)	
Off-pump	592 (69.7%)	391 (68.4%)	

DM, diabetes mellitus; HbA1c, glycated hemoglobin A1c.

$p = 0.036$). In particular, the incidence of deep sternal wound infection was higher in the DM group (2.0%) than in the non-DM group (1.1%) although this did not reach statistical significance ($p = 0.163$). The cause of death in the DM group was predominantly related to infection (10/18: 56%), while in the non-DM group there was only one patient who died of infection (1/6: 17%). On multivariate logistic regression analyses, the statistically significant risk factors for the

Table 2 Adverse events and outcomes.

	DM group ($n = 849$)	Non-DM group ($n = 572$)	Risk ratio (95% CI)	p-Value
Primary composite endpoint[a]	105 (12.4%)	60 (10.5%)	1.18 (0.87–1.59)	0.279
Additional composite endpoint[b]	92 (10.8%)	42 (7.3%)	1.48 (1.04–2.09)	0.027
All-cause deaths	18 (2.1%)	6 (1.1%)	2.02 (0.81–5.06)	0.124
Acute myocardial infarction	11 (1.3%)	12 (2.1%)		NA
Related death	2 (0.2%)	0		NA
Cerebrovascular accident	12 (1.4%)	6 (1.1%)		NA
Related death	1 (0.1%)	0		
Other cardiovascular event	11 (1.3%)	15 (2.6%)		NA
Related death	3 (0.4%)	1 (0.2%)		
All infections	78 (9.2%)	35 (6.1%)	1.50 (1.02–2.21)	0.036
Related death	10 (1.2%)	1 (0.2%)		
Infection site				
Deep sternal wound	17 (2.0%)	6 (1.1%)	1.91 (0.76–4.81)	0.163
Superficial sternal wound	22 (2.6%)	15 (2.6%)		
Graft harvest site	22 (2.6%)	9 (1.6%)		
Blood stream	5 (0.6%)	2 (0.4%)		
Urinary tract	5 (0.6%)	1 (0.2%)		
Pneumonia	9 (1.1%)	8 (1.1%)		
Acute renal failure	12 (1.4%)	5 (0.9%)	1.62 (0.57–4.57)	0.359
Related death	1 (0.1%)	0		
Other deaths	1 (0.1%)	4 (0.7%)		NA

CI, confidence interval; DM, diabetes mellitus; NA, not available due to too few events.

[a] Primary composite endpoint consisted of acute myocardial infarction, cerebrovascular accidents, other cardiovascular events, overall infection and their related deaths.

[b] Additional composite endpoint consisted of overall infection, acute renal failure, and all-cause deaths.

Table 3 Multivariate logistic regression analysis for the primary composite endpoint.[a]

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.07	0.75–1.53	0.715
Age (in 10-year increments)	1.01	0.83–1.23	0.915
Male gender	0.58	0.40–0.86	0.006
Body mass index (in 1 kg/m^2 increments)	1.04	0.98–1.09	0.164
Congestive heart failure	1.01	0.58–1.70	0.985
Renal insufficiency	2.18	1.36–3.43	0.001
Chronic obstructive pulmonary disease	1.73	0.98–2.95	0.051
Peripheral artery disease	1.12	0.73–1.69	0.585
Left ventricular ejection fraction < 50%	1.25	0.83–1.86	0.268
Urgent	1.71	0.95–2.97	0.065
Emergency	0.79	0.22–2.24	0.689
Bilateral internal thoracic artery use	1.34	0.94–1.91	0.105
Intraoperative steroid use	0.72	0.49–1.06	0.100

CI, confidence interval.

[a] Primary composite endpoint consisted of acute myocardial infarction, cerebrovascular accidents, other cardiovascular events, overall infection and their related deaths.

Table 4 Multivariate logistic regression analysis for the additional composite endpoint.[a]

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.28	0.85–1.92	0.235
Age (in 10-year increments)	1.01	0.81–1.26	0.935
Male gender	0.58	0.38–0.89	0.012
Body mass index (in 1 kg/m^2 increments)	1.07	1.02–1.14	0.012
Congestive heart failure	0.94	0.51–1.67	0.843
Renal insufficiency	3.23	2.00–5.14	0.000
Chronic obstructive pulmonary disease	1.91	1.02–3.41	0.034
Peripheral artery disease	0.94	0.57–1.49	0.787
Left ventricular ejection fraction < 50%	1.39	0.89–2.13	0.139
Urgent	1.60	0.82–2.95	0.149
Emergency	1.13	0.34–3.13	0.823
Bilateral internal thoracic artery use	1.31	0.89–1.94	0.177
Intraoperative steroid use	0.66	0.42–1.01	0.060

CI, confidence interval.

[a] Additional composite endpoint consisted of overall infection, acute renal failure, and all-cause death.

Table 5 Multivariate logistic regression analysis for all infections.

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.29	0.84–2.01	0.253
Age (in 10-year increments)	0.96	0.76–1.22	0.751
Male gender	0.52	0.33–0.83	0.005
Body mass index (in 1 kg/m^2 increments)	1.08	1.02–1.14	0.014
Congestive heart failure	0.96	0.49–1.79	0.904
Renal insufficiency	3.13	1.86–5.16	0.000
Chronic obstructive pulmonary disease	1.85	0.93–3.46	0.064
Peripheral artery disease	0.85	0.49–1.40	0.533
Left ventricular ejection fraction < 50%	1.42	0.88–2.26	0.142
Urgent	1.37	0.65–2.69	0.386
Emergency	0.72	0.16–2.36	0.619
Bilateral internal thoracic artery use	1.37	0.90–2.09	0.144
Intraoperative steroid use	0.68	0.42–1.06	0.099

CI, confidence interval.

Table 6 Multivariate logistic regression analysis for all-cause death.

Variables	Odds ratio	95% CI	*p*-Value
Diabetes mellitus	1.89	0.72–5.61	0.219
Age (in 10-year increments)	1.10	0.67–1.88	0.715
Male gender	0.66	0.25–1.97	0.429
Body mass index (in 1 kg/m^2 increments)	0.90	0.78–1.04	0.169
Congestive heart failure	2.27	0.69–7.03	0.165
Renal insufficiency	3.04	1.12–7.80	0.023
Chronic obstructive pulmonary disease	4.22	1.24–12.60	0.013
Peripheral artery disease	1.56	0.55–4.07	0.374
Left ventricular ejection fraction < 50%	2.33	0.92–5.87	0.071
Urgent	3.15	0.89–10.32	0.065
Emergency	5.30	1.05–26.7	0.043
Bilateral internal thoracic artery use	1.85	0.71–4.81	0.204
Intraoperative steroid use	0.35	0.10–1.00	0.073

CI, confidence interval.

primary composite endpoint included female gender and renal insufficiency (Table 3). The statistically significant risk factors for the additional composite endpoint included female gender, BMI, renal insufficiency, and chronic obstructive pulmonary disease (Table 4). Also, the statistically significant risk factors for overall infection were female gender, BMI, and renal insufficiency (Table 5). Finally, the statistically significant preoperative or operative risk factors for all-cause death were renal insufficiency, congestive heart failure, and emergency surgery (Table 6). The presence of DM was not identified as a statistically significant independent risk factor on multivariate analyses for the composite endpoints and complications including overall infection and all-cause death which were linked to DM on the univariate analyses. On the other hand, it became apparent that preoperative renal insufficiency was a very strong common risk factor for both overall infection and all-cause death.

Discussion

In 2009, the Society of Thoracic Surgeons Blood Glucose Management Task Force published their guidelines regarding BG management during adult cardiac surgery [13]. According to these guidelines, it is highly desirable to maintain BG < 180 mg/dl during surgery and during the immediate postoperative period with intravenous insulin infusion in DM patients. Although it is unnecessary to use intravenous continuous insulin infusion in non-DM patients during surgery, both DM and non-DM patients benefit from maintaining BG < 180 mg/dl in order to prevent morbidity and mortality [13]. This begs the question of how low the target should be. Furnary et al. reported from their prospective observational study that there was a highly significant relationship between mortality and postoperative glucose levels rising above 175 mg/dl [10]. Our current BG levels in DM patients were barely below this cut-off value, given the intraoperative and postoperative 3-day average BG were 172 mg/dl and 168 mg/dl, respectively. Therefore, there seemed to be some room to lower the BG levels further, which potentially would reduce the morbidity and the mortality in the DM patients.

It has been reported that the presence of DM in patients undergoing CABG is a significant risk factor for hospital mortality and morbidity including stroke, deep sternal wound infection, and length of hospital stay from the STS database analyses [14]. In addition, DM patients have worse long-term survival than non-DM patients after surgery [6]. Our results from univariate analyses show that DM has a significant influence on the additional composite endpoint consisting of all-cause death, overall infection, and acute renal failure (10.8% vs 7.3%, $p = 0.027$). Looking at each complication, overall infection was the most significant factor contributing to this result (9.2% in DM group vs 6.1% in non-DM group, $p = 0.036$). Also, DM patients tended to have higher mortality than non-DM patients (2.1% vs 1.1%, $p = 0.124$). Moreover, DM patients tended to have a much higher incidence of deep sternal wound infection than non-DM patients (2.0% vs 1.1%, $p = 0.163$), although this difference did not reach statistical significance. However, the complication of infection definitely influenced mortality rates because the majority of deaths were related to infection in the DM group. There is no doubt that DM patients have unfavorable baseline characteristics such as diffuse coronary artery disease, peripheral artery disease, high BMI, and worse preoperative renal function, all of which would contribute to worse short- and long-term outcomes compared to non-DM patients.

Our multivariate logistic regression analyses failed to identify DM as an independent risk factor for any of the complications including overall infection and all-cause death. This is most likely because some other preoperative risk factors such as renal insufficiency (predominantly in the DM group) and chronic obstructive pulmonary disease (predominantly in the non-DM group) had too much influence to each endpoint, which attenuated the impact of the presence of DM. This is one of the well-known downsides of the logistic regression models. In fact, the prevalence of preoperative renal insufficiency in this study population is much higher (13.8% in the DM group) than that of other studies published in the literature [10]. It should also be noted that 85 patients (5.6% of all study patients) predominantly in the

DM group had been on chronic hemodialysis preoperatively, which must have given great impact to the multivariate analyses. We are now in the process of doing a sub-analysis in this regard to identify the relative impact of the presence of preoperative renal insufficiency.

The Portland Diabetic Project, which is an on-going prospective study of over 5000 DM patients, aims to show that tight glucose control from the end of surgery until the 2nd postoperative day with continuous insulin infusion may eliminate the diabetic disadvantage [15]. They showed that tight glucose control with a full 3 days of continuous insulin infusion (the Portland Protocol) significantly reduced mortality (by 65%), deep sternal wound infection (by 63%), and length of hospital stay (average 2-day reduction). Therefore, they concluded that DM is not the true risk factor for the seemingly unfair diabetic disadvantage in terms of increased mortality and morbidity. Since we showed that DM patients still have excess mortality and morbidity compared to non-DM patients in the current study, we might be able to reduce these excess complications by implementing tighter glucose control protocols.

It has been debated whether intensive BG control is better than conventional BG control. In a landmark paper, van den Berghe et al. conducted the first prospective randomized trial comparing tight BG control (target 80–110 mg/dl) with intensive insulin therapy to conventional BG control in critically ill surgical patients [16]. They demonstrated that tight BG control resulted in a significant reduction in mortality (10.6% with intensive treatment vs 20.2% with conventional treatment, $p = 0.005$), exclusively in those patients who required ≥ 5 days of intensive care unit (ICU) care with multiorgan failure and sepsis. Also, cardiac surgical mortality was reduced in those patients requiring ≥ 3 days of ICU care. D'Alessandro et al. reported a propensity analysis that showed that strict BG control significantly reduced the EuroSCORE expected mortality in DM patients undergoing CABG, especially in moderate- to high-risk patients [17]. Their BG target in the operating room and ICU were 150–200 mg/dl and ≤ 140 mg/dl, respectively. In terms of long-term outcomes, Lazar et al. showed that tight perioperative glucose control with glucose-insulin-potassium solution improved not only perioperative outcomes, but also long-term survival and freedom from recurrent angina [18]. These studies clearly demonstrate the superiority of tight BG control over conventional control, especially in critically ill patients. On the other hand, Gandhi et al. showed in a prospective randomized study on 400 patients undergoing CABG, including non-DM patients, that intraoperative intensive insulin therapy with a target range of 80–100 mg/dl did not reduce perioperative mortality and morbidity, but rather increased stroke rate and mortality [19]. Furthermore, a meta-analysis of 29 randomized studies focusing on the benefits and risks of tight glucose control in critically ill adult patients concluded that tight glucose control was not associated with significantly reduced hospital mortality but was associated with an increased risk of hypoglycemia [20]. To support these results, a recent prospective randomized multicenter trial (the NICE-SUGAR study) demonstrated that intensive BG control with a target of 81–108 mg/dl increased mortality among adults in the ICU compared with conventional BG control with a target of 180 mg/dl or less [21]. In this study, however, the mortalities in the intensive control group and conventional control group were 27.5% and 24.9% at 90 days after randomization, respectively. In both groups, potentially life-sustaining treatments were withheld or withdrawn in more than 90% of the patients who died. Also, it seems that severe hypoglycemia commonly occurred in the intensive BG control group of the study, which may raise the question of the safety and feasibility of the tight glucose control protocol itself. Because these patients in the study were so sick at the time of enrollment, it is difficult to compare the results of these studies with studies on regular cardiac surgery patients, given the current acceptable mortality after CABG of around 1–2%. It may be necessary to conduct a prospective randomized study to compare tight glucose control and conventional glucose control using more sophisticated protocols with a minimum risk of hypoglycemia in exclusively cardiac surgery patients to reach a definitive conclusion, which we are currently planning to initiate as a next step to our ultimate goal.

Perhaps, one of the other interesting features of this multi-center study is the fact that about 70% of all isolated CABG procedures were performed using the off-pump technique in both the DM and non-DM groups. This trend is far above the typical rates in North America, given the fact that the adoption of off-pump CABG was only 21.8% in 2009 according to the STS database [22]. A systematic review and meta-analysis of propensity score analyses in more than 123,000 patients comparing off-pump and on-pump CABG demonstrated that off-pump provides favorable outcomes in mortality, stroke, renal failure, wound infection, blood transfusion, intraaortic balloon pump support, and prolonged ventilation [23]. It will be interesting to see the impact of off-pump techniques in DM patients in terms of not only preoperative, intraoperative, and postoperative glucose control, but also in terms of postoperative complications and related mortality [24]. We are also planning to perform a post hoc subgroup analysis focusing on this in the near future.

There are several limitations to this study. This was a retrospective, observational study, and hence unknown patient selection processes may cause a bias. Importantly, there was no standard BG control protocol across the participating hospitals. Our sample size was relatively large, however, it was not large enough to stratify the level of perioperative BG control as an indicator of risk events. In fact, we were unable to show any difference in terms of the morbidity and mortality according to the level of intraoperative and postoperative BG control due to too few complications.

Conclusions

DM patients had poor perioperative BG control and higher incidence of infection with a higher mortality rate than non-DM patients. These results highlight the need to initiate prospective studies to standardize perioperative BG control protocols to obtain strict BG control, which may yield better surgical outcomes in Japanese DM patients undergoing cardiac surgery.

Acknowledgments

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Appendix I. The list of the participating surgical centers

Iwate Medical University Hospital, Sakakibara Heart Institute, Jichi Medical University Hospital, Nagoya University Hospital, Handa City Hospital, University Hospital of Kyoto Prefectural University of Medicine, Kyoto University Hospital, Tominaga Hospital, Wakayama Medical University Hospital, Kobe University Hospital, Kobe City Medical Center General Hospital, Kawasaki Medical School Hospital, Kurume University Hospital, Kagoshima University Hospital.

Appendix II.

Preoperative variables include age, gender, height, and weight. Preoperative co-morbidities included systemic hypertension, dyslipidemia, insulin-controlled diabetes mellitus (DM), oral medication-controlled DM, diet-controlled-DM, congestive heart failure, renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease, cigarette smoking, cerebrovascular accidents, and advanced New York Heart Association functional class. Cardiovascular variables included left main coronary disease, number of diseased coronary arteries, left ventricular ejection fraction, unstable angina, acute myocardial infarction (MI), previous MI, history of atrial fibrillation and ventricular tachycardia or fibrillation, cardiogenic shock, percutaneous coronary intervention, and intra-aortic balloon pump insertion. Preoperative blood laboratory variables included random and fasting serum glucose, glycated hemoglobin A1c, albumin, serum creatinine, blood urea nitrogen, total cholesterol, high-density and low-density lipoproteins, triglycerides, and C-reactive protein. Preoperative medications included digitalis, beta-blockers, nitrates, inotropic agents, oral hypoglycemics, insulin, diuretics, steroids, and immunosuppressants. Intraoperative variables were operative status (elective, urgent, or emergency), reoperative procedure, single or bilateral internal thoracic artery or other arterial conduit usage, saphenous vein grafts and their targets, use of cardiopulmonary bypass, application of aortic cross-clamping, aortic cross-clamp time, cardiopulmonary bypass time, administration of intravenous insulin and steroids, and blood transfusion.

Appendix III. Definitions of clinical events

Acute myocardial infarction: the presence of at least two of the following symptoms or findings:

(1) Creatine kinase (CK)-MB $\geq 5\%$ of total CK and total CK $\geq 3\times$ normal control, or CK-MB ≥ 100 mg/dl.
(2) Typical symptoms.
(3) Typical electrocardiographic (ECG) change (new onset of ST-T change in more than 2 consecutive leads on 12-lead ECG or abnormal Q wave).
(4) New onset abnormal wall motion abnormality lasting $\geq$24 h on echocardiography.

Of note, a pathological diagnosis of acute MI on autopsy does not require any of the above findings.

Cerebral infarction: including all the following symptoms and findings:

(1) Apparent focal neurological deficits and symptoms or signs compatible with no other identified causes.
(2) Neurological symptoms and signs lasting $\geq$24 h (excluded if patient died).
(3) Radiological diagnosis on computed tomography or magnetic resonance image.

Acute renal failure: increased creatinine of more than twice the preoperative baseline and equal to or more than 2.0 mg/dl, or newly requiring hemodialysis.

Infection: infection occurs within 30 days after surgery

1. *Deep sternal wound infection*: infection involving deep sternum and/or anterior mediastinum (fascia, sternum, mediastinum) and either:
   (1) Purulent drainage from the deep incision or the chest tube which is placed in the area communicating to the anterior mediastinum.
   (2) Organisms isolated from an aseptically obtained culture of fluid or tissue from the deep sternal wound or anterior mediastinum.
   (3) A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38 °C), localized pain, or tenderness, unless site is culture-negative.
   (4) An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
   (5) Diagnosis of a deep incisional surgical site infection by a surgeon or attending physician.
2. *Superficial sternal wound infection*: infection involving only the skin or subcutaneous tissue of the incision and either:
   (1) Purulent drainage, with or without laboratory confirmation, from the superficial incision.
   (2) Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
   (3) At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is

deliberately opened by surgeon, unless the incision is culture-negative.

   (4) Diagnosis of superficial incisional surgical site infection by the surgeon or attending physician.

3. *Graft harvest site infection*: surgical site(s) infection including saphenous vein and radial artery harvesting:
   (1) At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat.
   (2) Superficial incision is deliberately opened by the surgeon, or required resection of tissue or drainage, unless the incision is culture-negative.
   (3) Diagnosis of superficial incisional surgical site infection by the surgeon or attending physician.
4. *Blood stream infection*: the presence of a positive non-contaminated blood culture.

   Contamination is diagnosed if one or more of the following organisms is identified in only one of a series of blood cultures: coagulase-negative staphylococci; *Propionibacterium acnes*; *Micrococcus* species; ''viridans''-group streptococci; *Corynebacterium* species; or *Bacillus* species.
5. *Urinary tract infection*: defined as the presence of symptoms or signs compatible with no other identified source of infection along with either:
   (1) $>10^5/\mathrm{mm}^3$ colony forming units/ml of at least one bacterial species in a single urine specimen.
   (2) purulent urine (>10 white blood cells/field in a microscopic urinalysis).
6. *Pneumonia*: The clinical suspicion of pneumonia is based on clinical criteria; new or progressive radiological pulmonary infiltrate plus more than two of the following characteristics: temperature ($38\,^\circ\mathrm{C} <$ or $< 35.5\,^\circ\mathrm{C}$), leukocyte count ($>12{,}000\,\mathrm{cells/mm}^3$ or $<4000\,\mathrm{cells/mm}^3$) or purulent respiratory secretions. Ventilator-associated pneumonia is diagnosed in patients with microbiologic evaluation including the collection of at least one lower respiratory airway sample by sputum, tracheobronchial aspirate, bronchoscopy or by blind bronchoalveolar lavage. Blood cultures and cultures of pleural fluid specimens, if puncture was indicated, were also undertaken. Microbiologic confirmation of pneumonia was defined by the presence of ≥ 1 potentially pathogenic microorganism in the respiratory samples above the predefine thresholds (for bronchoalveolar lavage specimens, $>10^4$ colony forming units/ml; for sputum or tracheobronchial aspirate specimens, $>10^5$ colony forming units/ml); in pleural fluid specimens; or in blood cultures, if an alternative cause of bacteremia was ruled out.

Appendix IV.

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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

For editorial comment see p 285.

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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]

	No. (%)	
Characteristics	Advanced Airway Management (n = 281 522)	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.

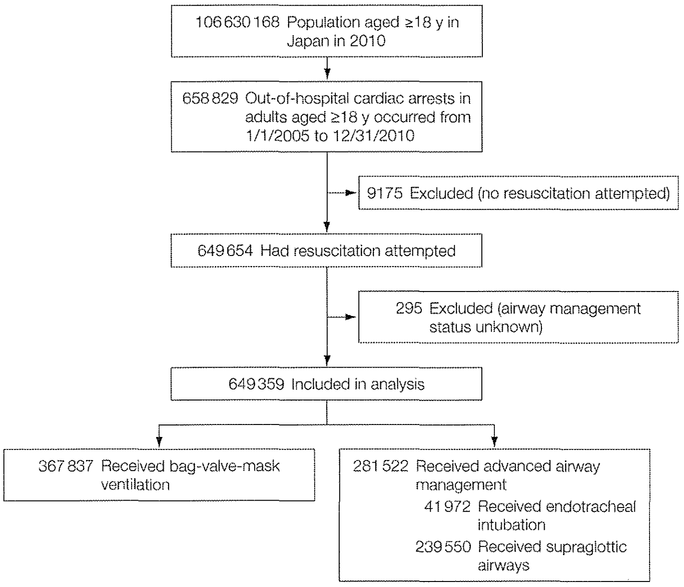
[a] Data are expressed as No. (%) of population unless otherwise indicated. All baseline characteristic comparisons between the 2 groups were statistically significant at $P<.001$.

[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 endpoint 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		Endotracheal Intubation		Supraglottic Airway	
			No. (%)	OR (95% CI) vs Bag-Valve-Mask[b]	No. (%)	OR (95% CI) vs Bag-Valve-Mask[b]	No. (%)	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.

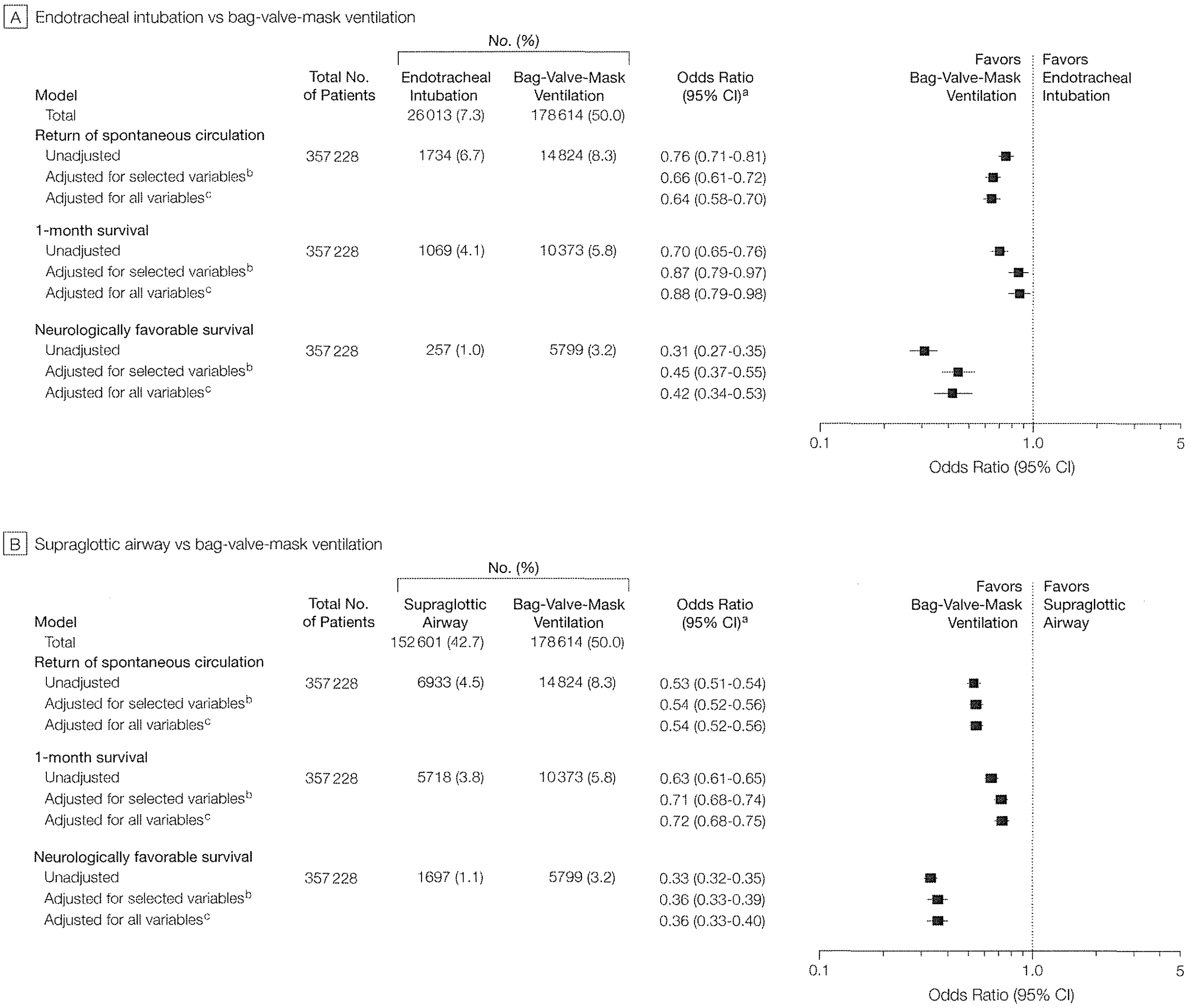
[a] Data are expressed as No. (%) of population unless otherwise indicated.

[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		26013 (7.3)	178614 (50.0)	
Return of spontaneous circulation				
Unadjusted	357228	1734 (6.7)	14824 (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	357228	1069 (4.1)	10373 (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	357228	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		152601 (42.7)	178614 (50.0)	
Return of spontaneous circulation				
Unadjusted	357228	6933 (4.5)	14824 (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	357228	5718 (3.8)	10373 (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	357228	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.
Administrative, technical, or material support: Brown.
Study supervision: Hasegawa, Hiraide, Brown.
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