EDITORIAL

Whether to Intubate During Cardiopulmonary Resuscitation
Conventional Wisdom vs Big Data

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For 60 years, health care professionals and lay bystanders have saved the lives of individuals with cardiac arrest through successful deployment of cardiopulmonary resuscitation (CPR). Although the 2010 American Heart Association CPR guidelines changed from the traditional "ABC" (airway-breathing-circulation) to "CAB" (circulation-airway-breathing) to ensure that rescue personnel are not unduly distracted from the prompt provision of optimal chest compressions, the core elements have largely remained unchanged.[1] The definitive approach to secure and protect the airway and hence deliver effective breathing is via emergency endotracheal intubation by a suitably trained professional followed by institution of artificial ventilation. If no individual skilled in endotracheal intubation is available, then airway management via a bag-valve-mask device is an acceptable interim alternative. Because of the large number of in-hospital cardiac arrests, hospitals arrange, often at considerable cost, to have around-the-clock emergency response teams capable of providing advanced cardiac life support (ACLS), including endotracheal intubation.

Related article

The American Heart Association engages in considerable efforts to generate and disseminate updated evidence-based guidelines for ACLS. Many elements of the guidelines are informed by randomized clinical trials (RCTs). However, certain aspects of resuscitation are not easy to evaluate in an RCT. Notably, there has been little enthusiasm to randomize patients to be managed with or without endotracheal intubation—the conventional wisdom is that this question has been asked and answered. Nonetheless, observational studies, paradoxically, have suggested that patients who are intubated have greater morbidity and mortality. The problem, of course, is that patients who are intubated may have greater severity of illness in the first place, and efforts to adjust for severity of illness may fail to fully account for residual indication bias.

Confounding by indication is arguably the major limitation to the use of observational data for estimation of treatment effects. However, as health care becomes digitized, there is now considerable optimism that advances in data richness and analytic techniques ("big data") will permit more reliable estimation of therapeutic effectiveness.[2] This optimism led to inclusion in the 21st Century Cures Act of an explicit mandate for the US Food and Drug Administration (FDA) to consider real-world evidence, and not just RCT results, during regulatory approval decisions.[3]

In this issue of *JAMA*, Andersen and colleagues[4] provide a highly sophisticated analysis of the benefits and harms of endotracheal intubation during CPR. Their approach and findings are instructive both for the provision of ACLS and as a window to what lies ahead as regulators, clinicians, and researchers envision incorporation of evidence of treatment effectiveness from actual clinical practice settings.

The authors conducted their analysis using the Get With The Guidelines-Resuscitation (GWTG-R) registry, which includes extremely detailed records of patients who sustained cardiac arrest at several hundred hospitals across the United States. Selecting from 668 hospitals over a 15-year period (January 2000 through December 2014), Andersen et al identified 108 079 adults who had a cardiac arrest managed with chest compressions, had complete data, did not have prior do-not-resuscitate orders, and were not already intubated. Of these patients, 71 615 (66.3%) were intubated within 15 minutes of their cardiac arrest. The primary analysis consisted of generating a paired case-control study, matching patients at the minute they were intubated following cardiac arrest to a control patient who was not intubated during that same minute using a "propensity to be intubated" model. The investigators were able to match 43 314 (60.5%) of the intubated patients to suitable control patients and found that the intubated patients incurred lower likelihood of return of spontaneous circulation (57.8% vs 59.3%; $P < .001$), a lower rate of good neurological outcome (10.6% vs 13.6%; $P < .001$), and worse survival (16.3% vs 19.4%; $P < .001$). Extensive sensitivity and secondary analyses largely confirmed the primary findings.

There are considerable strengths to this study. The data set is large, generalizable, and richly detailed with information to permit sophisticated risk adjustment. The use of time-based propensity matching captures an added level of detail missing in prior studies. However, even though the data were gathered prospectively and were subject to audit checks, some elements are inherently difficult to capture or missing. For example, the data set records intubation, but intubation can take several minutes, and the recorders may not capture the same moment in the process either consistently or accurately. Furthermore, the control patients are individuals who are not intubated during the same minute that a "case" was intubated. However, these controls may become "cases" in subsequent minutes. In other words, this is a comparison of those intubated vs those who are either never intubated or not intubated yet.

This kind of "now vs later" question is common in medicine, yet not that easy to study. For example, the ideal design would be to compare the outcomes of all patients for whom the clinician decides to intubate "now" vs those in the "maybe later" group. However, intent to intubate is not captured in the data. Therefore, Andersen et al were forced to define cases as patients who were successfully intubated, whereas patients for whom the intent to intubate was unsuccessful or took longer than expected ended up being in the pool of potential controls instead of cases. Data sets from clinical registries often lack critical nuance, such as what the clinician was thinking or wanted to do, and so researchers are forced to oversimplify the study question or design, with potentially important consequences. A solution in this instance could be to modify the data collection, but the existing data set took 15 years to accrue—waiting another 15 years for an updated analysis of even more detailed data is daunting.

So, should clinicians conclude that early intubation is harmful or, at least, ineffective and unnecessary? The act of intubation, especially in skilled hands, should not directly cause injury or death. However, distraction from effective chest compressions while intubation is performed could certainly be harmful. Intubation may also facilitate provision of higher oxygen concentrations, which have been associated with harm.[5] Moreover, patients in the "maybe later" group who recover without any intubation avoid the multiple potential complications of prolonged mechanical ventilation. But, an alternative explanation is that patients who were intubated had greater illness severity in ways for which the design did not account, despite the richness of the data. It is also possible that hospitals or physicians and other members of the resuscitation team with greater propensity to intubate patients are also more likely to provide other therapies or interventions that may inadvertently cause harm. The data set did not allow the authors to explore these possibilities more thoroughly.

In other words, intubation may or may not be harmful, although clear demonstration of benefit is lacking. This is hardly a ringing endorsement for such an established intervention that requires substantial cost to provide, considering both the training and staffing costs and the downstream costs of mechanical ventilation and intensive care that are incurred once the patient is intubated.

There are interesting implications from this study. First, it demonstrates that big data may not yet be big, or "rich," enough. Having data sets large enough and detailed enough to perform minute-by-minute time-based propensity matching exposes the crudeness, and vulnerability to unmeasured confounding, of past studies. Yet even data analyses of this size, detail, and sophistication are insufficient to exclude residual confounding. Second, study limitations notwithstanding, the lack of demonstrable benefit of intubation does challenge conventional wisdom, perhaps to the degree that would generate adequate equipoise for a future RCT. But, third, what would the RCT look like? The study by Andersen et al highlights that the consequences of a decision to intubate or not could change each minute during CPR, which means a clinically useful RCT likely would require multiple randomization points or treatment groups. For such a complicated RCT to be feasible, it should perhaps leverage the existing machinery of the GWTG-R registry to facilitate enrollment and lower data collection costs. Such an approach might appear counter to the hope that big data could supplant the RCT, but it was recently advocated by the FDA[6] and may be the only path to generate definitive evidence when analyses of big data generate findings at odds with conventional wisdom.

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REFERENCES

1. Field JM, Hazinski MF, Sayre MR, et al. Part 1: executive summary: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. *Circulation*. 2010;122(18)(suppl 3):S640-S656.

2. Weber GM, Mandl KD, Kohane IS. Finding the missing link for big biomedical data. *JAMA*. 2014;311(24):2479-2480.

3. Kesselheim AS, Avorn J. New "21st Century Cures" legislation: speed and ease vs science. *JAMA*. doi:10.1001/jama.2016.20640

4. Andersen LW, Granfeldt A, Callaway CW, et al; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Association between tracheal intubation during adult in-hospital cardiac arrest and survival. *JAMA*. doi:10.1001/jama.2016.20165

5. Kilgannon JH, Jones AE, Shapiro NI, et al; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010;303(21):2165-2171.

6. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence—what is it and what can it tell us? *N Engl J Med*. 2016;375(23):2293-2297.

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Association Between Tracheal Intubation During Adult In-Hospital Cardiac Arrest and Survival

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Editorial

Supplemental content

IMPORTANCE Tracheal intubation is common during adult in-hospital cardiac arrest, but little is known about the association between tracheal intubation and survival in this setting.

OBJECTIVE To determine whether tracheal intubation during adult in-hospital cardiac arrest is associated with survival to hospital discharge.

DESIGN, SETTING, AND PARTICIPANTS Observational cohort study of adult patients who had an in-hospital cardiac arrest from January 2000 through December 2014 included in the Get With The Guidelines–Resuscitation registry, a US-based multicenter registry of in-hospital cardiac arrest. Patients who had an invasive airway in place at the time of cardiac arrest were excluded. Patients intubated at any given minute (from 0-15 minutes) were matched with patients at risk of being intubated within the same minute (ie, still receiving resuscitation) based on a time-dependent propensity score calculated from multiple patient, event, and hospital characteristics.

EXPOSURE Tracheal intubation during cardiac arrest.

MAIN OUTCOMES AND MEASURES The primary outcome was survival to hospital discharge. Secondary outcomes included return of spontaneous circulation (ROSC) and a good functional outcome. A cerebral performance category score of 1 (mild or no neurological deficit) or 2 (moderate cerebral disability) was considered a good functional outcome.

RESULTS The propensity-matched cohort was selected from 108 079 adult patients at 668 hospitals. The median age was 69 years (interquartile range, 58-79 years), 45 073 patients (42%) were female, and 24 256 patients (22.4%) survived to hospital discharge. Of 71 615 patients (66.3%) who were intubated within the first 15 minutes, 43 314 (60.5%) were matched to a patient not intubated in the same minute. Survival was lower among patients who were intubated compared with those not intubated: 7052 of 43 314 (16.3%) vs 8407 of 43 314 (19.4%), respectively (risk ratio [RR] = 0.84; 95% CI, 0.81-0.87; *P* < .001). The proportion of patients with ROSC was lower among intubated patients than those not intubated: 25 022 of 43 311 (57.8%) vs 25 685 of 43 310 (59.3%), respectively (RR = 0.97; 95% CI, 0.96-0.99; *P* < .001). Good functional outcome was also lower among intubated patients than those not intubated: 4439 of 41 868 (10.6%) vs 5672 of 41 733 (13.6%), respectively (RR = 0.78; 95% CI, 0.75-0.81; *P* < .001). Although differences existed in prespecified subgroup analyses, intubation was not associated with improved outcomes in any subgroup.

CONCLUSIONS AND RELEVANCE Among adult patients with in-hospital cardiac arrest, initiation of tracheal intubation within any given minute during the first 15 minutes of resuscitation, compared with no intubation during that minute, was associated with decreased survival to hospital discharge. Although the study design does not eliminate the potential for confounding by indication, these findings do not support early tracheal intubation for adult in-hospital cardiac arrest.

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Mortality after adult in-hospital cardiac arrest remains high, and little is known about the effect of most interventions during cardiac arrest, including drugs and the use of advanced airway management.[1] Since 2010, guidelines have deemphasized the importance of tracheal intubation during cardiac arrest in adults, and the most optimal approach to airway management during cardiac arrest remains unknown.[1] The 2015 guidelines of both the American Heart Association and the European Resuscitation Council state that either a bag-valve-mask device or an advanced airway may be used for ventilation and oxygenation during cardiac arrest, and the guidelines make no distinction between the out-of-hospital and in-hospital setting.[2,3]

A large Japanese observational study of out-of-hospital cardiac arrest showed that advanced airway management was associated with a decreased chance of good outcome.[4] However, similar data are lacking for the in-hospital setting, where patient characteristics, the cause of cardiac arrest, the timing of interventions, the skills and experience of the health care professionals, and overall outcomes are significantly different.[1,5]

The aim of the current study was to evaluate the association between tracheal intubation during adult in-hospital cardiac arrest and survival to hospital discharge using the multicenter Get With The Guidelines–Resuscitation (GWTG-R) registry. This study also aimed to assess whether this association was modified by the first documented rhythm (shockable vs nonshockable) or other patient and event factors explored in prespecified subgroups.

Methods

Data Source

This study retrospectively analyzed data from the GWTG-R registry, a prospective quality improvement registry of in-hospital cardiac arrest in US hospitals; the registry is sponsored by the American Heart Association, which has regimented data collection methods and reliability checks.[6] Data are collected on all patients with in-hospital cardiac arrest who do not have prior do-not-resuscitate orders. Cardiac arrest is defined as pulselessness requiring chest compressions and/or defibrillation, with a hospital-wide or unit-based emergency response. Integrity of the data is ensured through online certification of data entry personnel and the use of standardized software.[7] Data from January 1, 2000, through December 31, 2014, were used. Hospital-level data were obtained from the American Hospital Association's Annual Survey from 2013.[8]

All participating hospitals are required to comply with local regulatory guidelines. Because data are used primarily at the local site for quality improvement, sites are granted a waiver of informed consent under the common rule. The Committee on Clinical Investigations at Beth Israel Deaconess Medical Center confirmed that this is not considered human subjects research under the common law and therefore waived the need for informed consent.

Patient Population

This study included adult patients (aged ≥18 years) with an index cardiac arrest for which they received chest compressions.

Key Points

Question Is tracheal intubation during adult in-hospital cardiac arrest associated with survival?

Findings In a study of 86 628 adults with in-hospital cardiac arrest using a propensity-matched cohort, tracheal intubation within the first 15 minutes was associated with a significantly lower likelihood of survival to hospital discharge compared with not being intubated (16.3% vs 19.4%, respectively).

Meaning These findings do not support early tracheal intubation for adult in-hospital cardiac arrest.

Patients who had an invasive airway in place at the time of the cardiac arrest (including tracheal tube, tracheostomy, laryngeal mask airway, or other invasive airways but not including nasopharyngeal or oropharyngeal airways) were not included. Hospital visitors and employees were not included. For the main analysis, patients with missing data on tracheal intubation, covariates (except race, for which a "not reported" category was created), and survival were excluded. This included patients with missing or inconsistent data on timing of tracheal intubation, timing of epinephrine administration, or timing of defibrillation (in those with a shockable rhythm). These patients were included after imputation of missing values in a preplanned sensitivity analysis (see "Statistical Analysis").

Race was included in the analysis because previous research has suggested that race might be associated with outcomes.[9] Race was self-reported by the patient or family or, if these were not available, by the clinical physician or institution. Race was reported as American Indian/Alaska Native, Asian, black or African American, Native Hawaiian/Pacific Islander, white, or unable to determine. Given small sample sizes in some groups, these were recategorized into white, black, other, and not reported.

Tracheal Intubation

Tracheal intubation was defined as insertion of a tracheal or tracheostomy tube during the cardiac arrest. The end of the cardiac arrest was when the patient had return of spontaneous circulation (ROSC) or when resuscitation was terminated without ROSC. Unsuccessful intubation attempts are not registered as intubations in the registry. The time to tracheal intubation was defined as the interval in whole minutes from loss of pulses until the tracheal tube was inserted. All times in the GWTG-R registry are collected in whole minutes. As such, a time to tracheal intubation of 0 minutes indicates that the tracheal intubation was performed within the same whole minute that pulses were lost, a time of 1 minute indicates that tracheal intubation was performed within the next whole minute, and so on.

Outcomes

The primary outcome was survival to hospital discharge. Secondary outcomes were ROSC and favorable functional outcome at hospital discharge. ROSC was defined as no further need for chest compressions (including cardiopulmonary bypass) sustained for at least 20 minutes. A cerebral performance category score of 1 (mild or no neurological deficit) or

2 (moderate cerebral disability) was considered a good functional outcome consistent with current Utstein guidelines.[10] The cerebral performance category score was determined by data abstractors reviewing the medical record. Abstractors assessing outcomes were not blinded to exposure status but were unaware of the hypothesis of the current study.

Statistical Analysis

The statistical analysis plan for the current study largely follows that of a recent, similar GWTG-R study in children.[11] Categorical variables are presented as counts (frequencies), and continuous variables are presented as medians (interquartile ranges [IQRs]). Independent categorical variables were compared with the χ^2 test, and the Cochran-Armitage test was used to test for trends in tracheal intubation over time.

To assess the adjusted association between tracheal intubation during cardiac arrest and survival to hospital discharge, this study used time-dependent propensity score matching.[12] This approach has previously been used in studies analyzing time-dependent cardiac arrest interventions,[11,13] and it is designed to account for the fact that the intubation procedure might not occur during the cardiac arrest if ROSC or termination of efforts occurs first. The propensity score was calculated based on a Cox proportional hazards model with intubation during the cardiac arrest as the dependent variable and with all variables included in **Table 1** as independent variables. Additional details are provided in the eAppendix in the Supplement.

Next, 1:1 risk set matching on the propensity score was performed using a nearest neighbor–matching algorithm with a maximum caliber of 0.01 of the propensity score. Patients being intubated at any given minute (from minute 0 to minute 15) were separately and sequentially propensity score matched with a patient who was at risk of being intubated within the same minute.[11] At-risk patients included those who were still undergoing resuscitation and were not intubated before or within the same minute. At-risk patients therefore also included patients who were intubated later, as the matching should not be dependent on future events.[11-14] As such, the matched group with no intubation includes patients who subsequently were intubated (although later than their matched counterpart). For additional details on the rationale for and interpretation of this type of analysis and matching, see the eAppendix in the Supplement.

To assess the performance of the matching, baseline characteristics were compared with standardized differences where a difference less than 0.1 is generally considered negligible.[15] Using the matched cohort, modified Poisson regression was performed to assess the association between tracheal intubation during cardiac arrest and survival to hospital discharge, obtaining risk ratios (RRs) with robust variance estimates.[16,17] To account for the matching and potential clustering within hospitals, generalized estimating equations were used as described by Miglioretti and Heagerty.[18] Results are reported from the regression models as RRs with 95% confidence intervals. The analysis was repeated for the secondary outcomes.

This study tested whether the association between tracheal intubation and survival to hospital discharge differed according to a number of prespecified subgroups: initial rhythm (shockable [pulseless ventricular tachycardia or ventricular fibrillation] vs nonshockable [asystole or pulseless electrical activity]), timing of the matching (0-4, 5-9, and 10-15 minutes), illness category, whether the patient had preceding respiratory insufficiency (see eTable 1 in the Supplement for definition), and the location of the event. Subgroup differences were tested by adding an interaction between the intubation variable and the subgroup variable of interest to the modified Poisson regression model in the propensity-matched cohort. As a post hoc analysis, this study also considered the interaction when treating timing of the matching as a continuous linear variable. To account for missing data, multiple imputations were performed as described in the eAppendix in the Supplement. As a post hoc analysis, we used non–time-dependent propensity score matching (see the eAppendix in the Supplement for details).

All hypothesis tests were 2-sided, with a significance level of $P < .05$. All secondary analyses should be considered exploratory as no adjustments were made for multiple comparisons.[19] Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc). The statistical analysis plan was outlined and agreed on by the entire author group before any analyses were performed unless stated otherwise.

Results

Patient Characteristics

The study population included 108 079 patients (**Figure 1**) from 668 hospitals. Baseline characteristics in the overall group and according to intubation are provided in Table 1. The median age was 69 years (IQR, 58-79 years), and 45 073 patients (42%) were female. Among the population, 75 579 patients (69.9%) were intubated, with 71 615 (66.3% of all patients and 94.8% of those intubated) intubated within the first 15 minutes. Over time, there was a decrease in the proportion of patients intubated within 15 minutes (70.0% in 2000 vs 63.6% in 2014; $P < .001$ for trend; eFigure 1 in the Supplement). The median time to tracheal intubation in those intubated within the first 15 minutes was 5 minutes (IQR, 3-8 minutes). The distribution of timing of intubation and the cumulative proportion of patients intubated over the first 15 minutes are provided in eFigure 2 in the Supplement. Of those intubated within the first 15 minutes, 336 (0.5%) received a tracheostomy. The intubation confirmation methods in those intubated are presented in eTable 2 in the Supplement, and drugs administered during the cardiac arrest other than epinephrine are listed in eTable 3 in the Supplement.

Among 88 749 patients with an initial nonshockable rhythm, 61 264 (69.0%) were intubated within 15 minutes, with a median time to intubation of 5 minutes (IQR, 3-8 minutes). Among 19 330 patients with an initial shockable rhythm, 10 351 (53.5%) were intubated within 15 minutes. The median time to intubation in these patients was 5 minutes (IQR, 3-8 minutes).

Overall Outcomes and Unadjusted Analyses

A total of 24 256 patients (22.4%) survived to hospital discharge. In the unadjusted analysis, patients intubated within the first 15 minutes had lower survival compared with those not intubated: 12 140 of 71 615 (17.0%) vs 12 116 of 36 464 (33.2%), respectively (RR = 0.58; 95% CI, 0.57-0.59; $P < .001$).

Table 1. Patient, Hospital, and Event Characteristics Among Patients With In-Hospital Cardiac Arrest Without vs With Intubation in the First 15 Minutes of Resuscitation in the Full Cohort

Characteristic	Patients, No. (%) Total (N = 108 079)	No Intubation (n = 36 464)	Intubation (n = 71 615)
Patient Characteristics			
Demographic			
Age, median (IQR), y	69 (58-79)	68 (56-78)	70 (59-80)
Sex			
Male	63 006 (58)	21 047 (58)	41 959 (59)
Female	45 073 (42)	15 417 (42)	29 656 (41)
Race			
White	76 731 (71)	26 208 (72)	50 523 (71)
Black	21 517 (20)	6836 (19)	14 681 (21)
Other	3398 (3)	1148 (3)	2250 (3)
Not reported	6433 (6)	2272 (6)	4161 (6)
Illness category			
Medical			
Cardiac	40 565 (38)	15 032 (41)	25 533 (36)
Noncardiac	48 318 (45)	14 856 (41)	33 462 (47)
Surgical			
Cardiac	6049 (6)	2383 (7)	3666 (5)
Noncardiac[a]	11 315 (10)	3414 (9)	7901 (11)
Trauma	1832 (2)	779 (2)	1053 (1)
Preexisting condition[b]			
Cardiac			
History of myocardial infarction	18 204 (17)	5830 (16)	12 374 (17)
Myocardial infarction this admission	17 477 (16)	6520 (18)	10 957 (15)
History of heart failure	24 830 (23)	7784 (21)	17 046 (24)
Heart failure this admission	19 446 (18)	6218 (17)	13 228 (18)
Noncardiac			
Respiratory insufficiency	37 474 (35)	12 951 (36)	24 523 (34)
Diabetes mellitus	35 075 (32)	11 081 (30)	23 994 (34)
Renal insufficiency	36 334 (34)	11 507 (32)	24 827 (35)
Metastatic or hematologic malignancy	13 572 (13)	4226 (12)	9346 (13)
Hypotension or hypoperfusion	22 135 (20)	7863 (22)	14 272 (20)
Pneumonia	13 456 (12)	4524 (12)	8932 (12)
Baseline depression in CNS function	11 312 (10)	3559 (10)	7753 (11)
Metabolic or electrolyte abnormality	15 696 (15)	5223 (14)	10 473 (15)
Septicemia	14 516 (13)	5204 (14)	9312 (13)
Acute CNS nonstroke event	6796 (6)	2205 (6)	4591 (6)
Hepatic insufficiency	7031 (7)	2273 (6)	4758 (7)
Acute stroke	4095 (4)	1343 (4)	2752 (4)
Major trauma	2623 (2)	1111 (3)	1512 (2)

(continued)

Table 1. Patient, Hospital, and Event Characteristics Among Patients With In-Hospital Cardiac Arrest Without vs With Intubation in the First 15 Minutes of Resuscitation in the Full Cohort (continued)

Characteristic	Patients, No. (%) Total (N = 108 079)	No Intubation (n = 36 464)	Intubation (n = 71 615)
Hospital Characteristics			
Bed size, No.			
1-249	20 083 (19)	7011 (19)	13 072 (18)
250-499	42 853 (40)	13 949 (38)	28 904 (40)
≥500	45 143 (42)	15 504 (43)	29 639 (41)
Teaching status			
Major	37 409 (35)	13 274 (36)	24 135 (34)
Minor	33 054 (31)	10 912 (30)	22 142 (31)
Nonteaching	37 616 (35)	12 278 (34)	25 338 (35)
Ownership			
Military	2218 (2)	774 (2)	1444 (2)
Nonprofit	77 690 (72)	26 076 (72)	51 614 (72)
Government	16 322 (15)	5738 (16)	10 584 (15)
Private	11 849 (11)	3876 (11)	7973 (11)
Location			
Rural	5774 (5)	1928 (5)	3846 (5)
Urban	102 305 (95)	34 536 (95)	67 769 (95)
Geographical location			
Northeast	15 190 (14)	5214 (14)	9976 (14)
Southeast	32 372 (30)	10 592 (29)	21 780 (30)
Midwest	22 856 (21)	7696 (21)	15 160 (21)
South central	22 069 (20)	7244 (20)	14 825 (21)
West	15 592 (14)	5718 (16)	9874 (14)
In-Hospital Cardiac Arrest Characteristics			
Year of cardiac arrest			
2000-2002	9973 (9)	2707 (7)	7266 (10)
2003-2004	15 522 (14)	4271 (12)	11 251 (16)
2005-2006	16 057 (15)	4701 (13)	11 356 (16)
2007-2008	16 154 (15)	5365 (15)	10 789 (15)
2009-2010	15 058 (14)	5486 (15)	9572 (13)
2011-2012	16 418 (15)	6702 (18)	9716 (14)
2013-2014	18 897 (17)	7232 (20)	11 665 (16)
In place at time of cardiac arrest			
Noninvasive assisted ventilation	11 117 (10)	8164 (22)	2953 (4)
Dialysis[c]	2912 (3)	944 (3)	1968 (3)
Implantable cardiac defibrillator	1913 (2)	539 (1)	1374 (2)
Intra-arterial catheter	4485 (4)	2209 (6)	2276 (3)
Electrocardiogram	80 864 (75)	30 069 (82)	50 795 (71)
Pulse oximeter	62 634 (58)	24 678 (68)	37 956 (53)
Vasoactive agents[d]	16 056 (15)	7822 (21)	8234 (12)
Antiarrhythmic agents[e]	3348 (3)	1641 (5)	1707 (2)

(continued)

Table 1. Patient, Hospital, and Event Characteristics Among Patients With In-Hospital Cardiac Arrest Without vs With Intubation in the First 15 Minutes of Resuscitation in the Full Cohort (continued)

Characteristic	Patients, No. (%) Total (N = 108 079)	No Intubation (n = 36 464)	Intubation (n = 71 615)
Location			
Emergency department	10 965 (10)	3695 (10)	7270 (10)
Floor with telemetry	22 215 (21)	6243 (17)	15 972 (22)
Floor without telemetry	27 249 (25)	6091 (17)	21 158 (30)
Intensive care unit	38 547 (36)	17 398 (48)	21 149 (30)
OR, PACU, or interventional unit	6471 (6)	2289 (6)	4182 (6)
Other[f]	2632 (2)	748 (2)	1882 (3)
Time of day			
Day, 7:00 AM to 10:59 PM	72 547 (67)	24 853 (68)	47 694 (67)
Night, 11:00 PM to 6:59 AM	35 532 (33)	11 611 (32)	23 921 (33)
Day			
Weekday, Monday 7 AM to Friday 11 PM	74 578 (69)	25 209 (69)	49 369 (69)
Weekend, Friday 11 PM to Monday 7 AM	33 501 (31)	11 255 (31)	22 246 (31)
Hospital-wide cardiac arrest response activated	89 561 (83)	28 597 (78)	60 964 (85)
Witnessed	84 473 (78)	30 788 (84)	53 685 (75)
First documented pulseless rhythm			
Asystole	39 119 (36)	11 607 (32)	27 512 (38)
Pulseless electrical activity	49 630 (46)	15 878 (44)	33 752 (47)
Ventricular fibrillation	12 569 (12)	5522 (15)	7047 (10)
Pulseless ventricular tachycardia	6761 (6)	3457 (9)	3304 (5)
Time to compressions, min			
0	98 949 (92)	33 648 (92)	65 301 (91)
1	4819 (4)	1559 (4)	3260 (5)
≥2	4311 (4)	1257 (3)	3054 (4)
Epinephrine administration	96 046 (89)	27 737 (76)	68 309 (95)
Time to epinephrine administration, median (IQR), min	2 (0-5)	1 (0-4)	2 (1-5)
Defibrillation[g]	17 479 (90)	8019 (89)	9460 (91)
Time to defibrillation, median (IQR), min	1 (0-3)	1 (0-2)	2 (0-4)

Abbreviations: CNS, central nervous system; IQR, interquartile range; OR, operating room; PACU, postanesthesia care unit.

[a] Includes patients with an obstetric admission (n = 135).

[b] See eTable 1 in the Supplement for definitions of preexisting conditions.

[c] Hemodialysis or peritoneal dialysis, continuous arteriovenous dialysis, or venovenous hemofiltration or dialysis.

[d] Dobutamine, dopamine (>3 µg/kg/min), epinephrine, nitroglycerin, norepinephrine, phenylephrine, vasopressin, and/or "other vasoactive agent(s)."

[e] Continuous infusion of amiodarone, lidocaine, procainamide, and/or "other antiarrhythmic(s)."

[f] Ambulatory and outpatient areas; delivery suite; rehabilitation, skilled nursing, and mental health facilities; same-day surgical areas; and "other."

[g] Includes only patients with a first documented pulseless rhythm of pulseless ventricular tachycardia or ventricular fibrillation.

Among the study population, 67 540 patients (62.5%) had ROSC (data were missing for 7 patients). The proportion of patients with ROSC was lower in those intubated within the first 15 minutes compared with those not intubated: 42 366 of 71 611 (59.2%) vs 25 174 of 36 461 (69.0%), respectively (RR = 0.75; 95% CI, 0.73-0.76; $P < .001$). A total of 4631 patients (4.3%) had missing data on functional outcome. Of the 103 448 patients without missing data on functional outcome, 16 504 (16.0%) had a good functional outcome. The proportion of patients with a good functional outcome was lower in those intubated within the first 15 minutes compared with those not intubated: 7717 of 69 212 (11.2%) vs 8787 of 34 236 (25.7%), respectively (RR = 0.55; 95% CI, 0.54-0.56; $P < .001$).

Time-Dependent Propensity Score–Matched Analysis

A total of 86 628 patients were included in the propensity-matched cohort (43 314 intubated patients [exposed group] matched 1:1 to 43 314 patients without intubation during the same minute [unexposed group], although these patients could have been intubated later). For patients in the exposed group, the median time to tracheal intubation was 4 minutes (IQR, 2-6 minutes). Among the unexposed group, 29 539 patients (68.2%) were intubated at some time point after the matching. For these patients, the time to intubation was 8 minutes (IQR, 5-12 minutes). Characteristics of the matched cohort according to exposure status are provided in **Table 2**. The patients were well matched on all included characteristics. In this matched cohort, survival was lower among the exposed group than among the unexposed group: 7052 of 43 314 (16.3%) vs 8407 of 43 314 (19.4%), respectively (RR = 0.84; 95% CI, 0.81-0.87; $P < .001$). The proportion of patients with ROSC was lower among the exposed group than among the unexposed group: 25 022 of 43 311 (57.8%) vs 25 685 of 43 310 (59.3%), respectively (RR = 0.97; 95% CI, 0.96-0.99; $P < .001$). Good functional outcome was also lower among the exposed group than among the unexposed group: 4439 of 41 868 (10.6%) vs 5672 of 41 733 (13.6%), respectively (RR = 0.78; 95% CI, 0.75-0.81; $P < .001$). The results are summarized in **Table 3**.

Subgroup Analyses

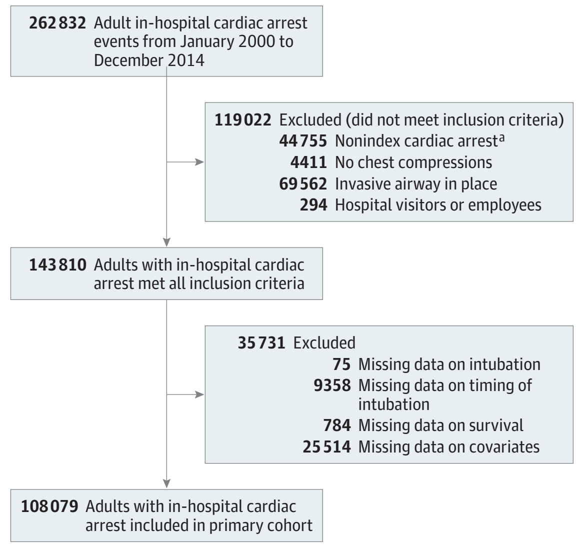
The results of the subgroup analyses for survival are presented in **Figure 2**. There was a significant interaction for initial rhythm ($P < .001$) such that tracheal intubation was more strongly associated with a lower likelihood of survival in those with an initial shockable rhythm (RR = 0.68; 95% CI, 0.65-0.72) compared with those with an initial nonshockable rhythm (RR = 0.91; 95% CI, 0.88-0.94). The association between tracheal intubation and survival was also modified by preexisting respiratory insufficiency (P for interaction < .001). In those without preexisting respiratory insufficiency, intubation was associated with lower likelihood of survival (RR = 0.78; 95% CI, 0.75-0.81), whereas no association was seen in those with preexisting respiratory insufficiency (RR = 0.97; 95% CI, 0.92-1.02). There were also subgroup differences according to illness category ($P < .001$) and location ($P = .002$) (Figure 2). There was no significant interaction for the time of matching ($P = .38$), indicating that the association between intubation and survival did not change during the first 15 minutes of the cardiac arrest. There was also no significant interaction when treating time of matching as a continuous linear variable ($P = .22$; eFigure 3 in the Supplement).

Sensitivity Analyses

Data were missing or inconsistent for at least 1 variable for 35 731 patients (24.8%), with a median number of missing variables of 0 (IQR, 0-0 variables; mean [SD], 0.5 [1.4] variables). A total of 143 810 patients were included in the sensitivity analysis accounting for missing data. Between 112 684 and 113 076 patients were propensity score matched in the 20 imputed data sets. The results from these analyses were similar to the primary analyses. Tracheal intubation was associated with lower likelihood of survival (RR = 0.84; 95% CI, 0.81-0.87; $P < .001$), ROSC (RR = 0.97; 95% CI, 0.97-0.98; $P < .001$), and good functional outcome (RR = 0.81; 95% CI, 0.79-0.84; $P < .001$).

In a post hoc analysis using non-time-dependent propensity score matching, 61 262 patients were matched. The patients were well matched on all included covariates (standardized differences between −0.03 and 0.03). In this cohort, intubation as compared with no intubation was associated with a lower likelihood of survival: 5968 of 30 631 patients (19.5%) vs 11 074 of 30 631 patients (36.2%), respectively (RR = 0.54; 95% CI, 0.52-0.56; $P < .001$). Intubation was also associated with a decreased likelihood of ROSC (18 885 of 30 629 intubated patients [61.7%] vs 21 465 of 30 628 patients not intubated [70.1%]; RR = 0.88; 95% CI, 0.87-0.89; $P < .001$) and a good functional outcome (3850 of 29 403 intubated patients [13.1%] vs 8129 of 28 669 patients not intubated [28.4%]; RR = 0.46; 95% CI, 0.44-0.48; $P < .001$).

Figure 1. Diagram of Derivation of the Study Population



[a] Cardiac arrests that were not the first cardiac arrest during the current admission.

Discussion

In this large, multicenter, retrospective, observational, matched cohort study, tracheal intubation at any minute within the first 15 minutes during in-hospital cardiac arrest, compared with no intubation during that minute, was associated with a 3% absolute reduction and 16% relative reduction in survival to hospital discharge. Intubation was also associated with a 2% absolute reduction and 3% relative reduction in ROSC and a 3% absolute reduction and 22% relative reduction in good functional outcome at hospital discharge.

Studies of tracheal intubation during adult in-hospital cardiac arrest are scarce, and no randomized clinical trials comparing intubation with no intubation in this setting were identified.[1,2] An observational study (n = 470) from 1990 of patients with in-hospital cardiac arrest found that tracheal intubation during the cardiac arrest was associated with increased mortality,[20] similar to an observational study from 2001 (n = 445).[21] A large observational study (n = 649 359) from Japan found that tracheal intubation during out-of-hospital cardiac arrest was associated with decreased odds of neurologically favorable survival.[4] However, an observational study (n = 32 513) from Korea found that intubation during out-of-hospital cardiac arrest was associated with good neurological outcome at hospital discharge.[22] In both studies, tracheal intubation was rare (6% and 4%, respectively) and rates of good outcome were low.[4,22] A meta-analysis from 2013 of observational out-of-hospital cardiac arrest studies found that tracheal intubation compared with basic airway management was not associated with ROSC but was associated with decreased survival.[23] None of these previous studies accounted for the time-dependent nature of tracheal intubation during cardiac arrest as done in the current study (see the eAppendix in the Supplement for additional discussion of the importance of this approach).

Table 2. Patient, Hospital, and Event Characteristics Among Patients With In-Hospital Cardiac Arrest Without vs With Intubation in the First 15 Minutes of Resuscitation in the Matched Cohort[a]

Characteristic	Patients, No. (%) No Intubation (n = 43 314)	Patients, No. (%) Intubation (n = 43 314)	Standardized Difference
Patient Characteristics			
Demographic			
Age, median (IQR), y	70 (58-79)	70 (58-80)	.014
Sex			
Male	25 332 (58)	25 486 (59)	.007
Female	17 982 (42)	17 828 (41)	.007
Race			
White	30 547 (71)	30 713 (71)	.008
Black	8837 (20)	8710 (20)	.007
Other	1361 (3)	1321 (3)	.005
Not reported	2569 (6)	2570 (6)	<.001
Illness category			
Medical			
Cardiac	15 779 (36)	15 716 (36)	.003
Noncardiac	19 979 (46)	20 017 (46)	.002
Surgical			
Cardiac	2274 (5)	2197 (5)	.008
Noncardiac[b]	4623 (11)	4708 (11)	.006
Trauma	659 (2)	676 (2)	.003
Preexisting condition[c]			
Cardiac			
History of myocardial infarction	7477 (17)	7370 (17)	.007
Myocardial infarction this admission	6786 (16)	6697 (15)	.006
History of heart failure	10 186 (24)	10 170 (23)	.001
Heart failure this admission	7852 (18)	7947 (18)	.006
Noncardiac			
Respiratory insufficiency	14 822 (34)	14 845 (34)	.001
Diabetes mellitus	14 264 (33)	14 334 (33)	.003
Renal insufficiency	14 893 (34)	14 739 (34)	.007
Metastatic or hematologic malignancy	5579 (13)	5663 (13)	.006
Hypotension or hypoperfusion	8659 (20)	8741 (20)	.005
Pneumonia	5381 (12)	5351 (12)	.002
Baseline depression in CNS function	4629 (11)	4636 (11)	.001
Metabolic or electrolyte abnormality	6300 (15)	6306 (15)	<.001
Septicemia	5598 (13)	5707 (13)	.007
Acute CNS nonstroke event	2708 (6)	2756 (6)	.005
Hepatic insufficiency	2837 (7)	2841 (7)	<.001
Acute stroke	1639 (4)	1652 (4)	.002
Major trauma	962 (2)	954 (2)	.001

(continued)

Table 2. Patient, Hospital, and Event Characteristics Among Patients With In-Hospital Cardiac Arrest Without vs With Intubation in the First 15 Minutes of Resuscitation in the Matched Cohort[a] (continued)

Characteristic	Patients, No. (%) No Intubation (n = 43 314)	Intubation (n = 43 314)	Standardized Difference
Hospital Characteristics			
Bed size, No.			
1-249	8132 (19)	8016 (19)	.007
250-499	17 367 (40)	17 444 (40)	.004
≥500	17 815 (41)	17 854 (41)	.002
Teaching status			
Major	14 747 (34)	14 609 (34)	.007
Minor	13 252 (31)	13 357 (31)	.005
Nonteaching	15 315 (35)	15 348 (35)	.002
Ownership			
Military	905 (2)	928 (2)	.004
Nonprofit	31 189 (72)	31 195 (72)	<.001
Government	6444 (15)	6385 (15)	.004
Private	4776 (11)	4806 (11)	.002
Location			
Rural	2342 (5)	2348 (5)	.001
Urban	40 972 (95)	40 966 (95)	.001
Geographical location			
Northeast	6032 (14)	6077 (14)	.003
Southeast	13 184 (30)	13 123 (30)	.003
Midwest	9090 (21)	9160 (21)	.004
South central	8977 (21)	8898 (21)	.005
West	6031 (14)	6056 (14)	.002
In-Hospital Cardiac Arrest Characteristics			
Year of cardiac arrest			
2000-2002	4319 (10)	4480 (10)	.012
2003-2004	6783 (16)	6642 (15)	.009
2005-2006	6691 (15)	6824 (16)	.008
2007-2008	6484 (15)	6486 (15)	<.001
2009-2010	5837 (13)	5709 (13)	.009
2011-2012	5965 (14)	6030 (14)	.004
2013-2014	7235 (17)	7143 (16)	.006
In place at time of cardiac arrest			
Noninvasive assisted ventilation	2296 (5)	2377 (5)	.008
Dialysis[d]	1185 (3)	1176 (3)	.001
Implantable cardiac defibrillator	827 (2)	780 (2)	.008
Intra-arterial catheter	1455 (3)	1417 (3)	.005
Electrocardiogram	31 224 (72)	31 059 (72)	.008
Pulse oximeter	23 623 (55)	23 524 (54)	.005
Vasoactive agents[e]	5430 (13)	5426 (13)	<.001
Antiarrhythmic agents[f]	1123 (3)	1093 (3)	.004

(continued)

Table 2. Patient, Hospital, and Event Characteristics Among Patients With In-Hospital Cardiac Arrest Without vs With Intubation in the First 15 Minutes of Resuscitation in the Matched Cohort[a] (continued)

Characteristic	Patients, No. (%) No Intubation (n = 43 314)	Patients, No. (%) Intubation (n = 43 314)	Standardized Difference
Location			
Emergency department	4422 (10)	4546 (11)	.009
Floor with telemetry	9342 (22)	9373 (22)	.002
Floor without telemetry	12 263 (28)	12 331 (28)	.003
Intensive care unit	13 556 (31)	13 384 (31)	.009
OR, PACU, or interventional unit	2585 (6)	2550 (6)	.003
Other[g]	1146 (3)	1130 (3)	.002
Time of day			
Day, 7:00 AM to 10:59 PM	28 953 (67)	28 878 (67)	.004
Night, 11:00 PM to 6:59 AM	14 361 (33)	14 436 (33)	.004
Day			
Weekday, Monday 7 AM to Friday 11 PM	29 809 (69)	28 886 (69)	.004
Weekend, Friday 11 PM to Monday 7 AM	13 505 (31)	13 428 (31)	.004
Hospital-wide cardiac arrest response activated	36 562 (84)	36 529 (84)	.002
Witnessed	32 884 (76)	32 835 (76)	.003
First documented pulseless rhythm			
Asystole	16 324 (38)	16 574 (38)	.012
Pulseless electrical activity	20 344 (47)	20 065 (46)	.013
Ventricular fibrillation	4478 (10)	4501 (10)	.002
Pulseless ventricular tachycardia	2168 (5)	2174 (5)	.001
Time to compressions, min			
0	39 465 (91)	39 537 (91)	.006
1	1963 (5)	1931 (4)	.004
≥2	1886 (4)	1846 (4)	.005
Epinephrine administered before matching	23 084 (53)	23 226 (54)	.007
Time to epinephrine administration, median (IQR), min	1 (1-3)	1 (1-3)	.027
Defibrillation before matching[h]	3895 (59)	3859 (58)	.016
Time to defibrillation, median (IQR), min	1 (0-2)	1 (0-2)	.050

Abbreviations: CNS, central nervous system; IQR, interquartile range; OR, operating room; PACU, postanesthesia care unit.

[a] Patients being intubated at any given minute (from 0-15 minutes; intubation group) were matched with patients at risk of being intubated within the same minute (ie, still receiving resuscitation; no intubation group) based on a time-dependent propensity score calculated from multiple patient, event, and hospital characteristics.

[b] Includes patients with an obstetric admission (n = 110).

[c] See eTable 1 in the Supplement for definitions of preexisting conditions.

[d] Hemodialysis or peritoneal dialysis, continuous arteriovenous dialysis, or venovenous hemofiltration or dialysis.

[e] Dobutamine, dopamine (>3 μg/kg/min), epinephrine, nitroglycerin, norepinephrine, phenylephrine, vasopressin, and/or "other vasoactive agent(s)."

[f] Continuous infusion of amiodarone, lidocaine, procainamide, and/or "other antiarrhythmic(s)."

[g] Ambulatory and outpatient areas; delivery suite; rehabilitation, skilled nursing, and mental health facilities; same-day surgical areas; and "other."

[h] Includes only patients with a first documented pulseless rhythm of pulseless ventricular tachycardia or ventricular fibrillation.

Multiple mechanisms could explain a potential causal relationship between tracheal intubation and poor outcomes.[11,24] First, tracheal intubation might lead to a prolonged interruption in chest compressions.[25] Second, tracheal intubation might lead to hyperventilation and hyperoxia, which are associated with poor outcomes.[26,27] Third, tracheal intubation could delay other interventions such as defibrillation or epinephrine administration.[28,29] Fourth, delays in the time to success of intubation could result in inadequate ventilation or oxygenation by other means. Fifth, unrecognized esophageal intubation or dislodgement of the tube during the cardiac arrest could lead to fatal outcomes. Potential beneficial effects of intubation include better control of ventilation and oxygenation as well as protection from aspiration.[24] Moreover, once an advanced airway is established, chest compressions may be provided in a more continuous fashion.[30,31] However, continuous chest compressions may not improve outcomes.[32]

In this study, there were important differences in several prespecified subgroup analyses. Tracheal intubation was associated much more strongly with decreased survival among patients with an initial shockable rhythm (32% relative decrease) compared with those with an initial nonshockable rhythm (9% relative decrease). Similar subgroup differences have been reported in the out-of-hospital setting.[4] These findings may indicate that the potential detrimental effects of intubation are more pronounced in patients with a shockable rhythm, for whom other interventions such as early defibrillation are more relevant. The current study also identified an important subgroup difference accord-

Table 3. Outcomes for Patients With In-Hospital Cardiac Arrest Without vs With Intubation in the First 15 Minutes of Resuscitation in the Overall and Time-Dependent Propensity Score–Matched Cohorts

	Unadjusted Analysis			Propensity Score–Matched Analysis[a]		
	No. of Patients With Outcome/Total Patients (%)		Risk Ratio (95% CI)	No. of Patients With Outcome/Total Patients (%)		Risk Ratio (95% CI)
Outcome	No Intubation	Intubation		No Intubation	Intubation	
ROSC	25 174/36 461 (69.0)	42 366/71 611 (59.2)	0.75 (0.73-0.76)	25 685/43 310 (59.3)	25 022/43 311 (57.8)	0.97 (0.96-0.99)
Survival to hospital discharge	12 116/36 464 (33.2)	12 140/71 615 (17.0)	0.58 (0.57-0.59)	8407/43 314 (19.4)	7052/43 314 (16.3)	0.84 (0.81-0.87)
Favorable functional outcome[b]	8787/34 236 (25.7)	7717/69 212 (11.2)	0.55 (0.54-0.56)	5672/41 733 (13.6)	4439/41 868 (10.6)	0.78 (0.75-0.81)

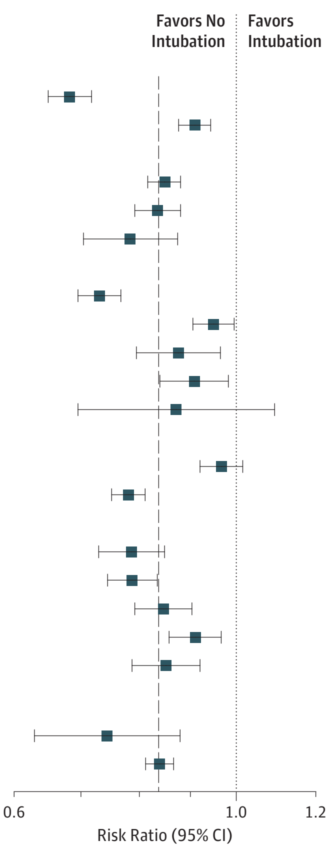
Abbreviation: ROSC, return of spontaneous circulation.

[a] Patients being intubated at any given minute (from 0-15 minutes; intubation group) were matched with patients at risk of being intubated within the same minute (ie, still receiving resuscitation; no intubation group) based on a time-dependent propensity score calculated from multiple patient, event, and hospital characteristics.

[b] A cerebral performance category score of 1 (mild or no neurological deficit) or 2 (moderate cerebral disability) at hospital discharge was considered a good functional outcome.

Figure 2. Forest Plot of Subgroup Analyses of Survival to Hospital Discharge in the Propensity-Matched Cohort

Subgroup	Survival to Hospital Discharge, No. of Patients With Outcome/Total Patients (%): Intubation	No Intubation	Risk Ratio (95% CI)	P Value for Interaction
Initial rhythm				
Shockable	1786/6675 (26.8)	2608/6646 (39.2)	0.68 (0.65-0.72)	<.001
Nonshockable	5266/36 639 (14.4)	5799/36 668 (15.8)	0.91 (0.88-0.94)	
Time of matching, min[a]				
0-4	4321/25 219 (17.1)	5098/25 219 (20.2)	0.85 (0.82-0.88)	
5-9	2248/14 937 (15.0)	2693/14 937 (18.0)	0.84 (0.79-0.88)	.38
10-15	483/3158 (15.3)	616/3158 (19.5)	0.78 (0.70-0.87)	
Illness category				
Medical cardiac	2697/15 716 (17.2)	3710/15 779 (23.5)	0.73 (0.70-0.77)	
Medical noncardiac	2695/20 017 (13.5)	2834/19 979 (14.2)	0.95 (0.91-1.00)	
Surgical cardiac	632/2197 (28.8)	747/2274 (32.8)	0.88 (0.80-0.96)	<.001
Surgical noncardiac	910/4708 (19.3)	984/4623 (21.3)	0.91 (0.84-0.98)	
Trauma	118/676 (17.5)	132/659 (20.0)	0.87 (0.79-1.09)	
Respiratory insufficiency[b]				
Yes	2546/14 845 (17.2)	2630/14 822 (17.7)	0.97 (0.92-1.02)	<.001
No	4506/28 469 (15.8)	5777/28 492 (20.3)	0.78 (0.75-0.81)	
Location				
Emergency department	914/4546 (20.1)	1131/4422 (25.6)	0.79 (0.73-0.85)	
Floor with telemetry	1570/9373 (16.8)	1987/9342 (21.3)	0.79 (0.74-0.83)	
Floor without telemetry	1432/12 331 (11.6)	1684/12 263 (13.7)	0.85 (0.79-0.90)	
Intensive care unit	2161/13 384 (16.1)	2406/13 556 (17.7)	0.91 (0.86-0.97)	.002
Operating room, postanesthesia care unit, or interventional unit	758/2550 (29.7)	903/2585 (34.9)	0.85 (0.79-0.92)	
Other	217/1130 (19.2)	296/1146 (25.8)	0.74 (0.63-0.88)	
Overall	7052/43 314 (16.3)	8407/43 314 (19.4)	0.84 (0.81-0.87)	



Risk ratios with 95% confidence intervals for predefined subgroup analyses. The *P* value represents the type III *P* value for the interaction between intubation and a given subgroup. The dashed vertical line represents the risk ratio in the overall cohort; the dotted vertical line, a risk ratio of 1.0 (ie, no effect). Except for the time of the matching, there were significant differences according to all other subgroups.

[a] The minute at which patients in the intubation group were intubated and matched with a patient not intubated before or within that same minute.

[b] Evidence of acute or chronic respiratory insufficiency within 4 hours up to the time of the event (see eTable 1 in the Supplement for additional details).

ing to preexisting respiratory insufficiency: intubation was not significantly associated with outcomes in those with preexisting respiratory insufficiency. A proportion of patients with preexisting respiratory insufficiency might have had cardiac arrest as a consequence of respiratory failure, and early advanced airway management could be beneficial for these patients. Although the effect estimate varied according to subgroup, intubation was not associated with improved survival in any of the subgroups.

A few relatively small randomized trials have been conducted in the out-of-hospital setting comparing various airway devices vs usual care or tracheal intubation, finding no differences in clinical outcomes between groups.[33-35] However, at least 3 currently ongoing randomized phase 3 trials are assessing advanced airway management during cardiac arrest in the out-of-hospital setting (clinicaltrials.gov identifiers NCT02419573 and NCT02327026 and isrctn.com identifier ISRCTN08256118). While these trials assess the efficacy of advanced airway management in the out-of-hospital setting, the results might not translate to the in-hospital setting given important differences in cardiac arrest etiology, skills of health care professionals, and timing of interventions. Given that intubation is very common during in-hospital cardiac arrest (70% in the current study) and that very little, if any, evidence exists to support this practice, randomized clinical trials in the in-hospital setting are needed and appear justified. However, based on the estimates from this study, such studies would likely need to be very large to be powered adequately to detect a significant difference.

The results of this study should be interpreted in relation to the observational design and certain limitations. Potential confounders such as the skills and experience of health care professionals, the underlying cause of the cardiac arrest, the quality of chest compressions, and the indication for intubation were not available in the registry. As such, confounding by indication could have influenced the results.[36] In the data registry, data on unsuccessful intubation attempts are not available. Limited published data are available on unsuccessful intubation in the global in-hospital setting. However, data from the emergency department[37] and out-of-hospital setting[38] indicate that failed intubation is associated with poor outcomes. Because these patients were classified as having no intubation in the GWTG-R registry, this would potentially bias the results toward the null and therefore probably cannot explain the findings reported herein. Misclassification of variables might have occurred, especially in relation to the timing of interventions.[39] However, it is most likely that these misclassifications are unrelated to outcomes[40] and therefore would be unlikely to explain the findings. In addition, although missing data were relatively uncommon in general (median of 0 missing variables [IQR, 0-0 missing variables] of more than 40 variables included), data were missing on at least 1 variable for 25% of the patients. This study aimed to address this by using multiple imputations techniques, which showed results similar to those of the primary analysis.

Conclusions

Among adult patients with in-hospital cardiac arrest, initiation of tracheal intubation within any given minute during the first 15 minutes of resuscitation, compared with no intubation during that minute, was associated with decreased survival to hospital discharge. Although the study design does not eliminate the potential for confounding by indication, these findings do not support early tracheal intubation for adult in-hospital cardiac arrest.

ARTICLE INFORMATION

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Author Contributions: Dr Andersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Andersen, Donnino.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Andersen, Kurth.
Supervision: All authors.

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REFERENCES

1. Callaway CW, Soar J, Aibiki M, et al; Advanced Life Support Chapter Collaborators. Part 4: advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. 2015;132(16)(suppl 1):S84-S145.

2. Link MS, Berkow LC, Kudenchuk PJ, et al. Part 7: adult advanced cardiovascular life support: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(18)(suppl 2):S444-S464.

3. Soar J, Nolan JP, Böttiger BW, et al; Adult Advanced Life Support Section Collaborators. European Resuscitation Council Guidelines for Resuscitation 2015: section 3: adult advanced life support. *Resuscitation*. 2015;95:100-147.

4. Hasegawa K, Hiraide A, Chang Y, Brown DF. Association of prehospital advanced airway management with neurologic outcome and survival in patients with out-of-hospital cardiac arrest. *JAMA*. 2013;309(3):257-266.

5. Fredriksson M, Aune S, Bång A, et al. Cardiac arrest outside and inside hospital in a community: mechanisms behind the differences in outcome and outcome in relation to time of arrest. *Am Heart J*. 2010;159(5):749-756.

6. Peberdy MA, Kaye W, Ornato JP, et al. Cardiopulmonary resuscitation of adults in the hospital: a report of 14720 cardiac arrests from the National Registry of Cardiopulmonary Resuscitation. *Resuscitation*. 2003;58(3):297-308.

7. Peberdy MA, Ornato JP, Larkin GL, et al; National Registry of Cardiopulmonary Resuscitation Investigators. Survival from in-hospital cardiac arrest during nights and weekends. *JAMA*. 2008;299(7):785-792.

8. American Hospital Association. AHA Annual Survey Database fiscal year 2013. 2014. https://www.ahadataviewer.com/book-cd-products/aha-survey/. Accessed July 21, 2015.

9. Chan PS, Nichol G, Krumholz HM, et al; American Heart Association National Registry of Cardiopulmonary Resuscitation (NRCPR) Investigators. Racial differences in survival after in-hospital cardiac arrest. *JAMA*. 2009;302(11):1195-1201.

10. Perkins GD, Jacobs IG, Nadkarni VM, et al; Utstein Collaborators. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein resuscitation registry templates for out-of-hospital cardiac arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. *Resuscitation*. 2015;96:328-340.

11. Andersen LW, Raymond TT, Berg RA, et al; American Heart Association's Get With The Guidelines–Resuscitation Investigators. Association between tracheal intubation during pediatric in-hospital cardiac arrest and survival. *JAMA*. 2016;316(17):1786-1797.

12. Lu B. Propensity score matching with time-dependent covariates. *Biometrics*. 2005;61(3):721-728.

13. Nakahara S, Tomio J, Takahashi H, et al. Evaluation of pre-hospital administration of adrenaline (epinephrine) by emergency medical services for patients with out of hospital cardiac arrest in Japan: controlled propensity matched retrospective cohort study. *BMJ*. 2013;347:f6829.

14. Li YP, Propert KJ, Rosenbaum PR. Balanced risk set matching. *J Am Stat Assoc*. 2001;96(455):870-882. doi:10.1198/016214501753208573

15. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46(3):399-424.

16. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706.

17. Zou GY, Donner A. Extension of the modified Poisson regression model to prospective studies with correlated binary data. *Stat Methods Med Res*. 2013;22(6):661-670.

18. Miglioretti DL, Heagerty PJ. Marginal modeling of nonnested multilevel data using standard software. *Am J Epidemiol*. 2007;165(4):453-463.

19. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990;1(1):43-46.

20. Tortolani AJ, Risucci DA, Rosati RJ, Dixon R. In-hospital cardiopulmonary resuscitation: patient, arrest and resuscitation factors associated with survival. *Resuscitation*. 1990;20(2):115-128.

21. Dumot JA, Burval DJ, Sprung J, et al. Outcome of adult cardiopulmonary resuscitations at a tertiary referral center including results of "limited" resuscitations. *Arch Intern Med*. 2001;161(14):1751-1758.

22. Kang K, Kim T, Ro YS, Kim YJ, Song KJ, Shin SD. Prehospital endotracheal intubation and survival after out-of-hospital cardiac arrest: results from the Korean nationwide registry. *Am J Emerg Med*. 2016;34(2):128-132.

23. Fouche PF, Simpson PM, Bendall J, Thomas RE, Cone DC, Doi SA. Airways in out-of-hospital cardiac arrest: systematic review and meta-analysis. *Prehosp Emerg Care*. 2014;18(2):244-256.

24. Benoit JL, Prince DK, Wang HE. Mechanisms linking advanced airway management and cardiac arrest outcomes. *Resuscitation*. 2015;93:124-127.

25. Maignan M, Koch FX, Kraemer M, et al. Impact of laryngeal tube use on chest compression fraction during out-of-hospital cardiac arrest: a prospective alternate month study. *Resuscitation*. 2015;93:113-117.

26. Aufderheide TP, Sigurdsson G, Pirrallo RG, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. *Circulation*. 2004;109(16):1960-1965.

27. Kilgannon JH, Jones AE, Shapiro NI, et al; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010;303(21):2165-2171.

28. Chan PS, Krumholz HM, Nichol G, Nallamothu BK; American Heart Association National Registry of Cardiopulmonary Resuscitation Investigators. Delayed time to defibrillation after in-hospital cardiac arrest. *N Engl J Med*. 2008;358(1):9-17.

29. Donnino MW, Salciccioli JD, Howell MD, et al; American Heart Association's Get With The Guidelines-Resuscitation Investigators. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. *BMJ*. 2014;348:g3028.

30. Yeung J, Chilwan M, Field R, Davies R, Gao F, Perkins GD. The impact of airway management on quality of cardiopulmonary resuscitation: an observational study in patients during cardiac arrest. *Resuscitation*. 2014;85(7):898-904.

31. Kramer-Johansen J, Wik L, Steen PA. Advanced cardiac life support before and after tracheal intubation—direct measurements of quality. *Resuscitation*. 2006;68(1):61-69.

32. Nichol G, Leroux B, Wang H, et al; ROC Investigators. Trial of continuous or interrupted chest compressions during CPR. *N Engl J Med*. 2015;373(23):2203-2214.

33. Goldenberg IF, Campion BC, Siebold CM, McBride JW, Long LA. Esophageal gastric tube airway vs endotracheal tube in prehospital cardiopulmonary arrest. *Chest*. 1986;90(1):90-96.

34. Rabitsch W, Schellongowski P, Staudinger T, et al. Comparison of a conventional tracheal airway with the Combitube in an urban emergency medical services system run by physicians. *Resuscitation*. 2003;57(1):27-32.

35. Benger J, Coates D, Davies S, et al. Randomised comparison of the effectiveness of the laryngeal mask airway supreme, i-gel and current practice in the initial airway management of out of hospital cardiac arrest: a feasibility study. *Br J Anaesth*. 2016;116(2):262-268.

36. Kyriacou DN, Lewis RJ. Confounding by indication in clinical research. *JAMA*. 2016;316(17):1818-1819.

37. Kim J, Kim K, Kim T, et al. The clinical significance of a failed initial intubation attempt during emergency department resuscitation of out-of-hospital cardiac arrest patients. *Resuscitation*. 2014;85(5):623-627.

38. Wnent J, Franz R, Seewald S, et al; German Resuscitation Registry Study Group. Difficult intubation and outcome after out-of-hospital cardiac arrest: a registry-based analysis. *Scand J Trauma Resusc Emerg Med*. 2015;23:43.

39. Peace JM, Yuen TC, Borak MH, Edelson DP. Tablet-based cardiac arrest documentation: a pilot study. *Resuscitation*. 2014;85(2):266-269.

40. Frisch A, Reynolds JC, Condle J, Gruen D, Callaway CW. Documentation discrepancies of time-dependent critical events in out of hospital cardiac arrest. *Resuscitation*. 2014;85(8):1111-1114.