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 fibrilla-tion] 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

262 832 Adult in-hospital cardiac arrest events from January 2000 to December 2014

119 022 Excluded (did not meet inclusion criteria)
44 755 Nonindex cardiac arrest[a]
4411 No chest compressions
69 562 Invasive airway in place
294 Hospital visitors or employees

143 810 Adults with in-hospital cardiac arrest met all inclusion criteria

35 731 Excluded
75 Missing data on intubation
9358 Missing data on timing of intubation
784 Missing data on survival
25 514 Missing data on covariates

108 079 Adults with in-hospital cardiac arrest included in primary cohort

[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. (%)		Standardized Difference
	No Intubation (n = 43 314)	Intubation (n = 43 314)	
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. (%)		Standardized Difference
	No Intubation (n = 43 314)	Intubation (n = 43 314)	
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. (%)		Standardized Difference
	No Intubation (n = 43 314)	Intubation (n = 43 314)	
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
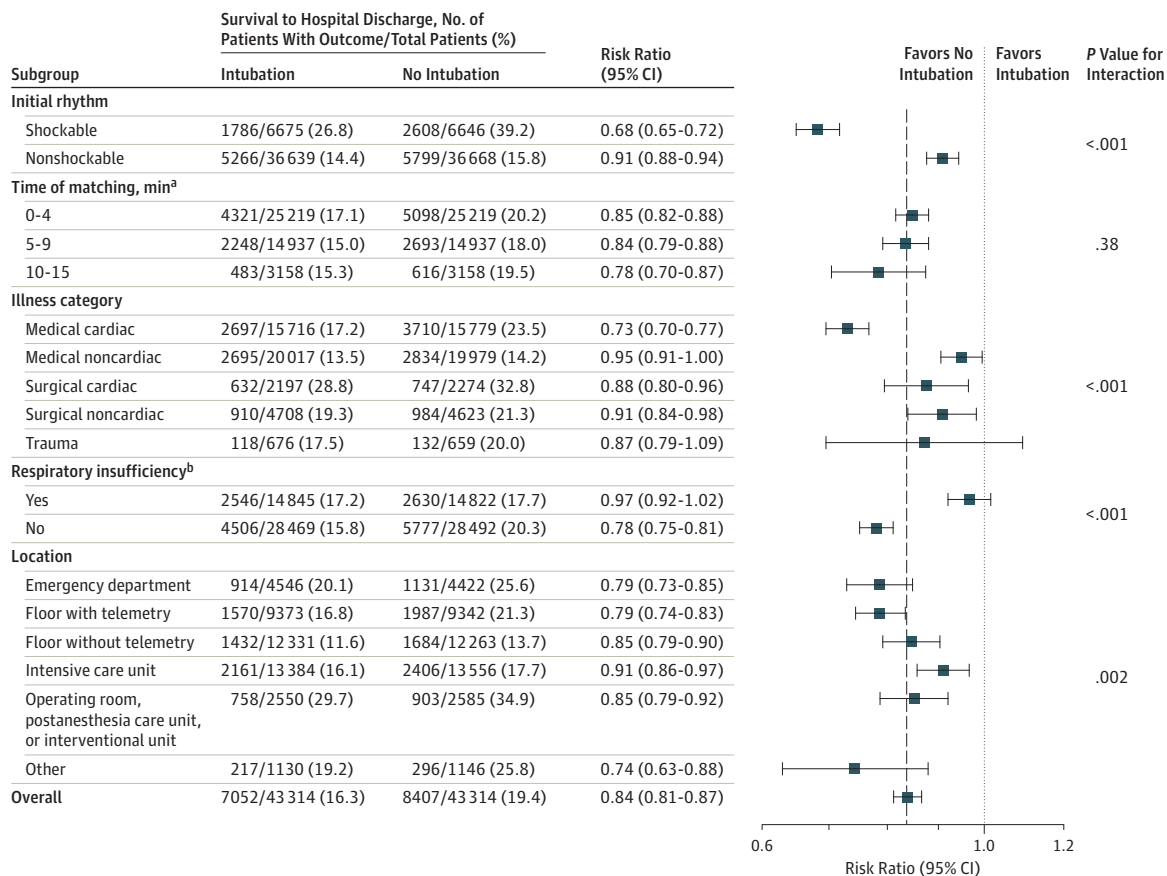
	Unadjusted Analysis			Propensity Score-Matched Analysis[a]		
	No. of Patients With Outcome/Total Patients (%)		Risk Ratio (95% CI)	No. of Patients With Outcome/Total Patients (%)		Risk Ratio (95% CI)
Outcome	No Intubation	Intubation		No Intubation	Intubation	
ROSC	25 174/36 461 (69.0)	42 366/71 611 (59.2)	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 (%)		Risk Ratio (95% CI)	P Value for Interaction
	Intubation	No Intubation		
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)	

Favors No Intubation / Favors Intubation

Risk Ratio (95% CI) — axis: 0.6, 1.0, 1.2

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 in-

tubation 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.

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Supplementary Online Content

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

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Supplemental Methods

Time-dependent propensity score calculation

The propensity score was calculated using a nonparsimonious multivariable Cox proportional hazards model. The outcome for the Cox model was time to intubation during the cardiac arrest. Patients were censored if the resuscitation ended (with or without return of spontaneous circulation [ROSC]) without intubation. All variables presented in Table 1 were included in the model including quadratic and cubic terms of age[1] and year as a categorical variable with each year a separate category. Since administration of epinephrine is associated with outcomes in in-hospital cardiac arrest[2,3], we entered receipt of the first epinephrine dose in the Cox model as a time-dependent covariate. The potential confounding effects of epinephrine could depend on the initial rhythm and we therefore also entered an interaction between epinephrine administration and the first documented rhythm to the model. Timing of the first defibrillation in patients with a shockable rhythm is also associated with outcomes[4]. For those with a shockable rhythm, we therefore entered the first defibrillation in the Cox model as a time-dependent covariate. We chose all variables *a priori* based on prior work[1,2,4-10] and/or clinical reasoning as well as availability in the GWTG-R registry. The propensity score for each patient was then derived from the Cox model as the hazard component (i.e. the linear predictor) at any given minute from the model.[11,12] The proportional hazards assumption was tested by including an interaction between each variable (except time-varying variables) and the natural logarithm of time. Given the large sample size, the proportional hazards assumption was determined to be met if the p-value from the interaction was > 0.01. Variables not meeting the proportional hazards assumption were included as time-varying covariates allowing the variables'

association with intubation to change every five minutes (i.e. different hazard ratios at $0 - 4$, $5 - 9$, and $10 - 15$ minutes).

Rationale for the time-dependent propensity score and risk set matching approach

Traditional propensity score matching allows for matching of exposed and unexposed patients based on a set of measured characteristics at a given point in time.[13,14] However, when covariates and the exposure (i.e. intubation) are time-dependent it is desirable that the distribution of covariates are balanced not only at baseline but also at any given time where the patients are at risk of the exposure.[11] For example, the risk of intubation (as quantified by the propensity score) might depend on whether or not the patient has received epinephrine. As receipt of epinephrine may also be associated with outcomes[2,3], it is essential that the exposed and unexposed patients are balanced on this covariate to avoid biased results. Simply adding a variable with yes vs. no epinephrine administration at any time during resuscitation is not optimal, as epinephrine might have been given after the intubation. Moreover, the association between a variable (e.g. location of the event) and intubation may vary over time. By allowing variables not meeting the proportional hazards assumption to vary over time, a more flexible model is created and we ensure that the exposed and unexposed are better balanced at any given time-point.

As also described elsewhere[3,12,15], the use of risk set matching is essential to reduce bias when assessing interventions during cardiac arrest. First, the duration of a cardiac arrest is associated with intubation i.e. the longer the cardiac arrest the higher the chance of the patient being intubated. As such, if one were to simply compare intubated to nonintubated patients, this would essentially be comparing patients with longer vs. shorter duration of

cardiac arrest. As an extreme example, one could imagine that all patients were intubated at minute 10. The comparison of intubated vs. nonintubated patients would then be a comparison of patients with ROSC or termination of resuscitation < 10 minutes to patients with ROSC or termination of resuscitation ≥ 10 minutes. Since the duration of the cardiac arrest (i.e. time to ROSC) is strongly associated with outcomes[16,17] and termination without ROSC is rarely performed before 10 minutes this would create severely biased results. Secondly, since interventions during cardiac arrest including intubation could theoretically influence the duration of the cardiac arrest (e.g. intubation leading to rapid ROSC), one cannot simply adjust for the duration of the cardiac arrest as early ROSC could be a mediator of the potential effect of intubation on outcomes such as survival to hospital discharge.

Lastly, the practical importance of using risk set matching is evident from two observational studies regarding epinephrine administration in out-of-hospital cardiac arrest. The two studies used the same database but one used time-dependent propensity score matching[12] whereas the other used traditional propensity score matching[18], ultimately yielding differing results with important differences in the conclusions of the paper. While it is obviously unclear which study had the correct results, the findings do indicate that the concepts discussed above are not purely theoretical.

Interpretation of the effect estimates

The interpretation of the results from the analyses using time-dependent propensity scores and risk set matching is different from that obtained from traditional logistic regression or propensity score–matched analysis. The effect estimate (i.e. risk ratio) from the current

study should be interpreted as the risk of the outcome (e.g. survival) in a patient being intubated during cardiac arrest at a given minute (from 0 to 15) compared to a similar patient (based on characteristics at that minute) who was not intubated before or at that minute ("as yet untreated").[19] These "as yet untreated" patients include those being intubated at a later time point as well as patients never intubated. We believe this interpretation is more clinically relevant as a clinician might consider intubating a patient at any given minute with future events being unknown.[15] That said, the effect estimates obtained from this approach (assuming no confounding, no selection bias, and no information bias) would likely be closer to one (i.e. less of an effect) compared to a randomized controlled trial comparing intubation to strictly no intubation.

Multiple imputation

We performed multiple imputation assuming that the data were "missing at random".[20] Data were missing or inconsistent on at least one variable for 35,731 patients (25%) with a median number of missing variables of 0 (quartiles: 0, 0, mean: 0.5, standard deviation: 1.4). In order to account for this, missing values for intubation, categorical covariates, and the outcomes (ROSC, survival and good functional outcome) were imputed using the fully conditional specification method[21] and a total of 20 data sets were created[22]. Time to intubation and time to the end of resuscitation were then imputed for each of the 20 data sets using Poisson distributions and time to epinephrine/defibrillation was imputed using zero-inflated Poisson distributions for those receiving epinephrine/defibrillation.[3,23,24] We then performed the time-dependent propensity score matching and modified Poisson regression

on each of these 20 data sets and combined the results using SAS "proc mianalyze". For this analysis, we accounted for the matching and not hospital-level clustering.

Non–time-dependent propensity score matching

As a *post hoc* analysis, we conducted a non–time-dependent propensity score–matched analysis. For this analysis, the propensity score was calculated based on a logistic regression model with intubation within the first 15 minutes (but otherwise irrespective of timing) as the outcome. This model included all variables included in our main analysis except administration of epinephrine and receipt of defibrillation since these are time-dependent and therefore cannot be included in a meaningful way. Based on the propensity score, patients were then matched using a nearest neighbor-matching algorithm with a maximum caliber of 0.01 of the propensity score. After the matching, similar analyses were performed as for our time-dependent propensity score–matched cohort. However, as discussed above, this approach has important limitations and the results should be interpreted with caution.

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eTable 1. Definitions of Preexisting Conditions

Variable	Definition
History of myocardial infarction	Documented diagnosis of myocardial ischemia (acute coronary syndrome)/infarction prior to this admission
Myocardial infarction this admission	Documented diagnosis of myocardial ischemia (acute coronary syndrome)/infarction this admission.
History of heart failure	Documented diagnosis of congestive heart failure prior to this admission
Heart failure this admission	Documented diagnosis of congestive heart failure this admission prior to the cardiac arrest
Respiratory insufficiency	Evidence of acute or chronic respiratory insufficiency within 4 hours up to the time of the event, defined by any of the following: • PaO_2/FiO_2 ratio < 300 (in the absence of preexisting documented cyanotic heart disease) • PaO_2 < 60 mm Hg (in the absence of preexisting documented cyanotic heart disease) • SaO_2 < 90 % (in the absence of preexisting documented cyanotic heart disease) • $PaCO_2$, $EtCO_2$ or $TcCO_2$ > 50 mm Hg • Spontaneous respiratory rate > 40/min or < 5/min • Requiring noninvasive ventilation (e.g., bag-valve-mask, mask or nasal continuous/bi-level positive airway pressure, negative pressure ventilation)
Diabetes mellitus	Documented diagnosis of Type I or Type II diabetes mellitus
Renal insufficiency	Evidence of renal insufficiency prior to the event, defined by any of the following: • Requiring ongoing dialysis or extracorporeal filtration therapies • Creatinine > 2 mg/dL within 24 hours up to the time of the cardiac arrest
Metastatic/hematologic malignancy	Any solid tissue malignancy with evidence of metastasis, or any blood borne malignancy
Hypotension/hypoperfusion	Evidence of hypotension within 4 hours up to the time of the event, defined by any of the following: • Systolic blood pressure < 90 mm Hg or mean arterial pressure < 60 mm Hg • Vasopressor/inotropic requirement after volume expansion (except for dopamine ≤ 3 mcg/kg/min) • Intra-aortic balloon pump
Pneumonia	Documented diagnosis of active pneumonia, where antibiotics have not yet been started or the pneumonia is still being treated with antibiotics

eTable 1. Definitions of preexisting conditions (continued)

Variable	Definition
Baseline depression in central nervous system function	Evidence of chronically depressed central nervous system function including a motor, cognitive, or functional baseline deficit (at time of system entry)
Metabolic/electrolyte abnormality	Evidence of metabolic/electrolyte abnormality within 4 hours up to the time of the event, defined by any of the following: • Sodium < 125 or > 150 mEq/L • Potassium < 2.5 or > 6 mEq/L • pH < 7.3 or > 7.5 (arterial) • Lactate > 2.5 mmol/L, • Blood glucose < 60 mg/dL
Septicemia	Bloodstream infection where antibiotics have not yet been started or the infection is still being treated with antibiotics. Documentation of "presumed sepsis" without confirmatory positive blood cultures would not constitute septicemia
Acute central nervous system nonstroke event	Evidence of decreased mental status, delirium, or coma not due to acute stroke within 4 hours up to time of the event
Hepatic insufficiency	Evidence of hepatic insufficiency within 24 hours up to the time of the event, defined by any of the following: • Total bilirubin > 2 mg/dL and aspartate aminotransferase > 2 times normal • Cirrhosis
Acute stroke	Documented diagnosis during this hospitalization of stroke, ischemic stroke, or hemorrhagic stroke
Major trauma	Evidence of multi-system injury or single system injury associated with shock or altered mental status during this admission and prior to the cardiac arrest

eTable 2. Intubation Confirmation Method(s) in Those Intubated Within 15 Minutes

| Confirmation method	Intubation within 15 min (n = 70,279)[a]
Expired carbon dioxide detector	47,872 (68)
Flexible/fiberoptic laryngoscope	376 (1)
Esophageal detector device	485 (1)
Other (except auscultation)	50,189 (71)
None documented	5058 (7)

[a] Data missing on 1,336 patients

eTable 3. Documented Drugs Administered During the Cardiac Arrest Other Than Epinephrine

| Drug	All patients (n = 107,351)[a]
Vasoactive drugs other than epinephrine	
Norepinephrine	11,274 (11)
Phenylephrine	3314 (3)
Dobutamine	2371 (2)
Dopamine	19,519 (18)
Other vasopressor	2904 (3)
Antiarrhythmic drugs	
Amiodarone	18,256 (17)
Lidocaine	9051 (8)
Atropine	65,507 (61)
Procainamide	189 (0)
Adenosine	379 (0)
Others	
Sodium bicarbonate	52,383 (49)
Calcium chloride/carbonate	27,349 (25)
Dextrose bolus	6425 (6)
Magnesium sulfate	10,077 (9)

[a] Data missing on 728 patients

eFigure 1. Proportion of In-Hospital Cardiac Arrest Patients Intubated Within 15 Minutes Over Time
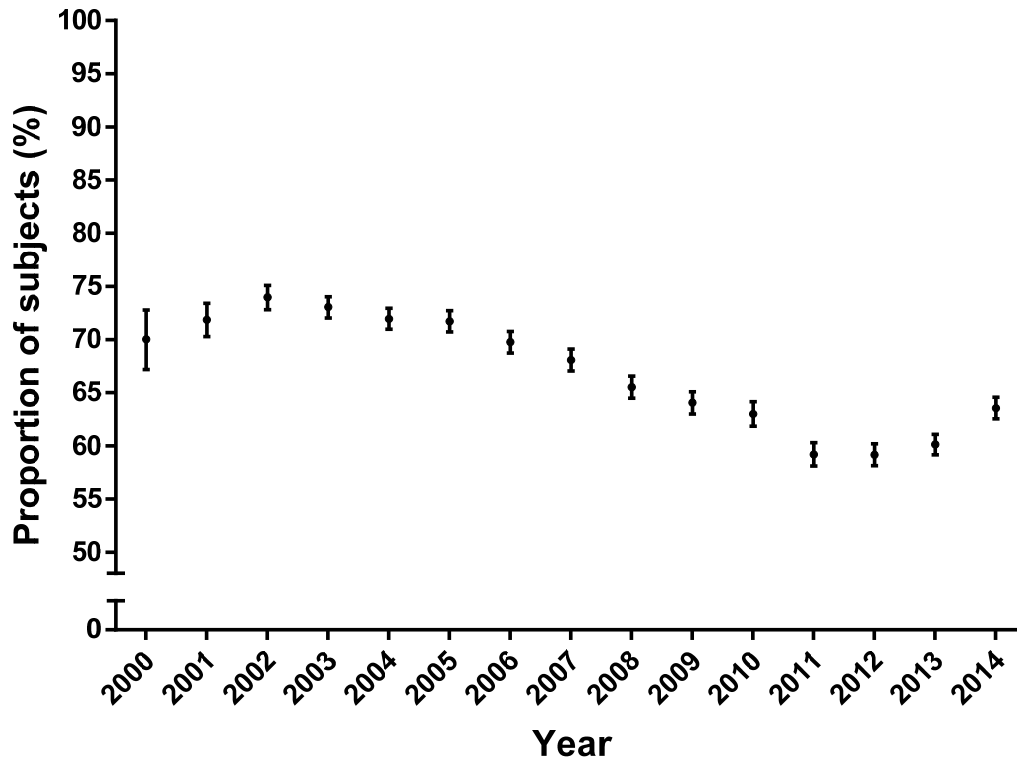
Proportion of patients with in-hospital cardiac arrest intubated within 15 minutes according to year. The error bars represent exact binomial 95% confidence intervals. There was a significant decrease in the proportion of patients intubated (p < 0.001 for trend).

eFigure 2. Distribution of Time to Intubation in Those Intubated (A) and Cumulative Proportion of Patients Intubated in the Entire Cohort (B)
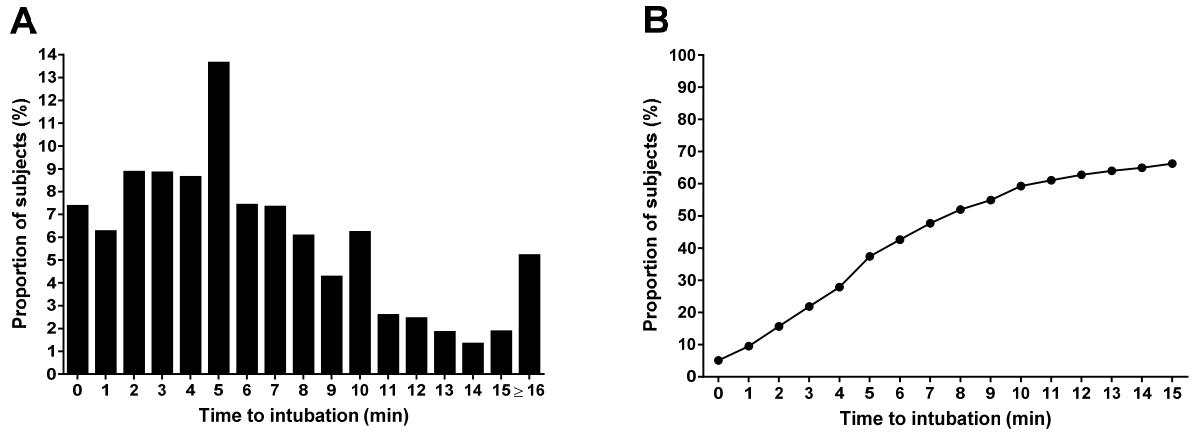
A: Distribution of the time to intubation in those intubated (n = 75,579). In those intubated within the first 15 minutes, the median time to intubation was 5 minutes (quartiles: 3, 8)

B: The cumulative proportion of patients intubated within the first 15 minutes in the full cohort (n = 108,079). 66% of all patients, corresponding to 95% of those intubated, were intubated within the first 15 minutes.

eFigure 3. Risk Ratios (A) and Survival to Hospital Discharge (B) Comparing Intubation to No Intubation According to the Time of Matching
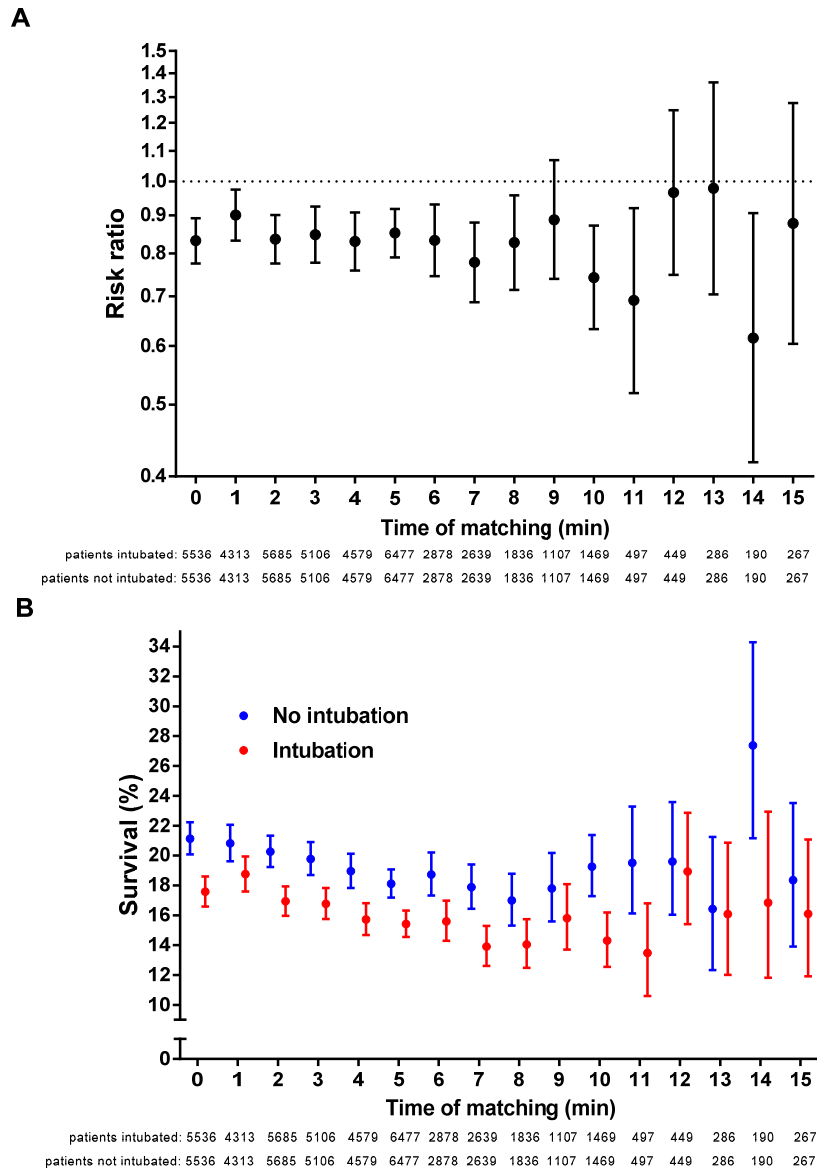
A: Risk ratios for the comparison of intubation to no intubation in the matched cohort according to the minute of matching for the outcome survival to hospital discharge. Values below one indicates that intubation was associated with decreased survival. When time of matching was treated as a linear continuous variable, there was no interaction between intubation and the time of matching (p = 0.22).

B: Survival to hospital discharge in the matched cohort according to intubation and minute of matching with 95% exact binomial confidence intervals.

The sample size for each minute is provided below the figure.