Association between tracheal intubation during adult in-hospital cardiac arrest and survival

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KEY POINTS

Question

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

Findings

In a retrospective cohort study of 86,628 adults 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 to not being intubated (16.3% vs 19.4%).

Meaning

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

ABSTRACT

Importance

Tracheal intubation is common during adult in-hospital cardiac arrest. However, 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

Observational study using prospectively collected data.

Setting

This retrospective cohort study used data from January 2000 to December 2014 from the *Get With The Guidelines® – Resuscitation* registry, a United States based multicenter registry of in-hospital cardiac arrest.

Participants

Adult patients with index in-hospital cardiac arrest. Patients who had an invasive airway in place at the time of the cardiac arrest were excluded.

Exposure

Tracheal intubation during the cardiac arrest.

Main outcomes and measures

The primary outcome was survival to hospital discharge. Secondary outcomes included return of spontaneous circulation and a good functional outcome. A cerebral performance category (CPC) score of 1 (mild or no neurological deficit) or 2 (moderate cerebral disability) was considered a good functional outcome. Patients being intubated at any given minute (from 0 to 15 minutes) were matched with patients at risk of being intubated within the same minute (i.e. still receiving resuscitation) based on a time-dependent propensity score calculated from multiple patient, event, and hospital characteristics.

Results

108,079 adult patients (median age 69 (58, 79) years, 45,073 (42%) female) were included from 668 hospitals. 71,615 patients (66%) were intubated within the first 15 minutes after cardiac arrest onset, and a total of 24,256 patients (22.4%) survived to hospital discharge. Among 86,628 patients included in the propensity-matched cohort, survival was lower in those intubated compared to those not intubated: 7052/43,314 (16.3%) vs. 8407/43,314 (19.4%), risk ratio: 0.84 (95%CI: 0.81, 0.87), $p < 0.001$. The proportion of patients with return of spontaneous circulation was lower in those intubated: 25,022/43,311 (57.8%) vs. 25,685/43,310 (59.3%), risk ratio: 0.97 (95%CI: 0.96, 0.99), $p < 0.001$. Good functional outcome was also lower in those intubated: 4439/41,868 (10.6%) vs. 5672/41,733 (13.6%), risk ratio: 0.78 (95%CI: 0.75, 0.81), p <

0.001. Although differences existed in pre-specified subgroup analyses, intubation was not associated with improved outcomes in any subgroup.

Conclusion and relevance

Among adult patients with in-hospital cardiac arrest, tracheal intubation during cardiac arrest compared with no intubation was associated with decreased survival to hospital discharge. Although the study design does not completely eliminate the potential for confounding by indication, these findings do not support early tracheal intubation for adult in-hospital cardiac arrest.

INTRODUCTION

Mortality after in-hospital adult 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 American Heart Association and the European Resuscitation Council 2015 guidelines state that either a bag-mask device or an advanced airway may be used for ventilation and oxygenation during cardiac arrest and makes 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 the arrest, the timing of interventions, provider skills and experience, 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 pre-specified subgroups.

METHODS

Data source

This study retrospectively analyzed data from the GWTG-R registry, which is a prospective, quality improvement registry of in-hospital cardiac arrest in United States hospitals sponsored by the American Heart Association, which has regimented data collection methods and reliability checks.[6] Data are collected on all in-hospital cardiac arrest patients 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 2000 to December 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, Boston, USA confirmed that this is not considered human subjects research under the common law and therefor waived the need for informed consent.

Patient population

This study included adult patients (≥ 18 years) with an index cardiac arrest receiving chest compressions. 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. Visitors/employees were not included. For the main analysis, patients with missing data on tracheal intubation, covariates (except for race where 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 pre-planned sensitivity analysis (see statistical analysis plan below).

Race was included in the analysis since previous research has suggested that race might be associated with outcomes.[9] Race was self-reported by the patient or family or if 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 re-categorized 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, etc.

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 (CPC) 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 CPC score was determined by data abstractors reviewing the medical record. Abstractors assessing outcomes were not explicitly 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 as medians (1st and 3rd quartiles). Independent categorical variables were compared with the Chi-Squared test and the Cochran–Armitage test was used to test for linear trends in tracheal intubation over time.

In order 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 is designed to account for the fact that the intubation procedure might not occur during the 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 all variables included in Table 1 as independent variables. Additional details are provided in the Supplemental Material.

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 still undergoing resuscitation and who 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 "no intubation" group will contain 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 Supplemental Material.

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 (RR) with robust variance estimates.[16,17] In order 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 RR with 95% confidence intervals (95%CI). 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 pre-specified subgroups: initial rhythm (shockable [pulseless ventricular tachycardia or ventricular fibrillation] vs. non-shockable [asystole or pulseless electrical activity]), timing of the matching (0 – 4, 5 – 9, and 10 – 15 minutes), illness category, whether or not the patient had preceding respiratory insufficiency (see eTable 1 in the Supplemental Material 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 Supplemental Material. As a post hoc additional analysis, we used non-time-dependent propensity score matching (see Supplemental Material for details).

All hypothesis tests were two-sided, with a significance level of $p < 0.05$. 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, Cary, NC, USA). The statistical analysis plan was outlined and agreed upon by the entire author group before any analyses were performed unless stated otherwise.

RESULTS

Patient characteristics

108,079 patients were included (see Figure 1) from 668 hospitals. Baseline characteristics in the overall group and according to intubation is provided in Table 1. In total, 75,579 patients (70%) were intubated, with 71,615 (66% of all patients and 95% of those intubated) intubated within the first 15 minutes. There was a decrease in the proportion of patients intubated within 15 minutes over time (70% in 2000 vs. 64% in 2014, $p < 0.001$ for linear trend, see eFigure 1 in the Supplemental Material). The median time to tracheal intubation in those intubated within the first 15 minutes was 5 minutes (quartiles: 3, 8). The distribution of timing of intubation and the cumulative proportion of patients intubated over the first 15 minutes are provided in eFigure 2 (Supplemental Material). Of those intubated within the first 15 minutes, 336 (0.5%) received a tracheostomy. The intubation confirmation method in those intubated is presented in eTable 2 (Supplemental Material) and drugs given during the cardiac arrest other than epinephrine are presented in eTable 3 (Supplemental Material).

In those with an initial non-shockable rhythm, 61,264 (69%) were intubated within 15 minutes with a median time to intubation of 5 minutes (quartiles: 3, 8). 10,351 patients (54%) with an initial shockable rhythm were intubated within 15 minutes. The median time to intubation in these patients were 5 minutes (quartiles: 3, 8).

Overall outcomes and unadjusted analyses

A total of 24,256 patients (22.4%) survived to hospital discharge. In the unadjusted analysis, those intubated within the first 15 minutes had lower survival when compared to those not intubated: 12,140/71,615 (17.0%) vs. 12,116/36,464 (33.2%), RR: 0.58 (95%CI: 0.57, 0.59), $p < 0.001$. 67,540 patients (62.5%) had ROSC (data was missing on seven patients). The proportion of patients with ROSC was lower in those intubated within the first 15 minutes: 42,366/71,611 (59.2%) vs. 25,174/36,461 (69.0%), RR: 0.75 (95%CI: 0.73, 0.76), $p < 0.001$. 4631 patients (4%) had missing data on functional outcome. Of those without missing data on functional outcome, 16,504 patients (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: 7717/69,212 (11.2%) vs. 8787/34,236 (25.7%), RR: 0.55 (95%CI: 0.54, 0.56), $p < 0.001$.

Time-dependent propensity score matched analysis

86,628 patients were included in the propensity-matched cohort. For patients in the intubated group, the median time to tracheal intubation was 4 minutes (quartiles: 2, 6). For patients in the "no intubation" group, 68% were intubated at some time point after the matching. For these patients the time to intubation was 8 minutes (quartiles: 5, 12). Characteristics of the matched cohort according to intubation is provided in Table 2. The patients were well matched on all included characteristics. In this matched cohort, survival was lower in those intubated compared to those not intubated: 7052/43,314 (16.3%) vs. 8407/43,314 (19.4%), RR: 0.84 (95%CI: 0.81, 0.87), $p < 0.001$. The proportion of patients with ROSC was lower in those intubated: 25,022/43,311 (57.8%) vs. 25,685/43,310 (59.3%), RR: 0.97 (95%CI: 0.96, 0.99), $p < 0.001$. Good functional outcome was also lower in those intubated: 4439/41,868 (10.6%) vs. 5672/41,733 (13.6%), RR: 0.78 (95%CI: 0.75, 0.81), $p < 0.001$. 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 ($p < 0.001$) 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 pre-existing respiratory insufficiency (p for interaction < 0.001). In those without pre-existing 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 pre-existing respiratory insufficiency (RR: 0.97 [95%CI: 0.92, 1.02]). There was also a subgroup differences according to illness category ($p < 0.001$) and location ($p = 0.002$), see Figure 2 for details. There was no significant interaction for the time of matching ($p = 0.38$) 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 ($p = 0.22$, see eFigure 3 in the Supplemental Material).

Sensitivity analyses

Data were missing or inconsistent for 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). 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 < 0.001), ROSC (RR: 0.97 [95%CI: 0.97, 0.98], p < 0.001), and good functional outcome (RR: 0.81 [95%CI: 0.79, 0.84], p < 0.001).

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 to no intubation was associated with a lower likelihood of survival: 5968/30,631 (19.5%) vs. 11,074/30,631 (36.2%), RR: 0.54 (95%CI: 0.52, 0.56), p < 0.001. Intubation was also associated with a decreased likelihood of ROSC: 18,885/30,629 (61.7%) vs. 21.465 (70.1%), RR: 0.88 (95%CI: 0.87, 0.89), p < 0.001 and a good functional outcome: 3850/29,403 (13.1%) vs. 8129/28,669 (28.4%), RR: 0.46 (95%CI: 0.44, 0.48), p < 0.001.

DISCUSSION

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

Studies of tracheal intubation during in-hospital adult 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 in-hospital cardiac arrest patients found that tracheal intubation during the cardiac arrest was associated with increased mortality[20] similarly to a 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 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 to 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 Supplemental Material for additional discussion of the importance of this approach).

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/oxygenation by other means. Lastly, 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] That said, continuous chest compressions may not improve outcomes.[32]

In the current study, there were important differences in several pre-specified subgroup analyses. Tracheal intubation was associated much more strongly with decreased survival in those with an initial shockable rhythm (32% relative decrease) compared with those with an initial non-shockable rhythm (9% relative decrease). Similar subgroup differences have been found 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 where other interventions such as early defibrillation are more relevant. The current study also found an important subgroup difference according to pre-existing respiratory insufficiency where intubation was not significantly associated with outcomes in those with pre-existing respiratory insufficiency. A proportion of those with pre-existing respiratory insufficiency might have had a cardiac arrest as a consequence of respiratory failure where early advanced airway management could be beneficial. 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 to usual care or tracheal intubation finding no differences in clinical outcomes between groups.[33-35] However, at least three randomized phase III trials are currently ongoing assessing advanced airway management during cardiac arrest in the out-of-hospital setting (clinicaltrials.gov: NCT02419573 and NCT02327026, isrctn.com: 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, rescue personnel skills, 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 the current study, such studies would likely need to be very large in order to be powered adequately to detect a significant difference.

The results of the current study should be interpreted in relation to the observational design and certain limitations. Potential confounders such as rescue personnel skills/experience, the underlying cause of the 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 are not available on unsuccessful intubation attempts. 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. Since these patients were classified as “no intubation” in the GWTG-R registry, this would potentially bias the results towards the null and therefore probably cannot explain the findings reported here. Misclassification of variables might have occurred especially related to the timing of interventions.[39] However, it is most likely that these misclassifications are undifferentiated (i.e. unrelated to outcomes)[40] and therefore would unlikely to explain the findings. In addition, although missing data were relatively uncommon in general (median 0 [quartiles: 0, 0] missing variables out of more than 40 variables included), data were missing on at least one variable for

25% of the patients. This study aimed to address this by utilizing multiple imputations techniques, which showed similar results as the primary analysis.

CONCLUSION

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

AUTHOR CONTRIBUTIONS AND ACKNOWLEDGEMENTS

Andersen had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. Andersen and Donnino were responsible for study concept and design. Andersen and Donnino were responsible for acquisition of data and drafting of the manuscript. Andersen conducted the statistical analysis. All authors critically revised the manuscript for important intellectual content and approved the final version for submission.

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Table 1. Patient, Hospital, and Event Characteristics in the Full Cohort[a]			
	All Patients (n = 108,079)	**No intubation ≤ 15 min (n = 36,464)**	**Intubation ≤ 15 min (n = 71,615)**
Demographics			
Age – median years (quartiles)	69 (58, 79)	68 (56, 78)	70 (59, 80)
Sex – no. (%)			
Male	63,006 (58)	21,047 (58)	41,959 (59)
Female	45,073 (42)	15,417 (42)	29,656 (41)
Race – no. (%)			
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 – no. (%)			
Medical – cardiac	40,565 (38)	15,032 (41)	25,533 (36)
Medical – non-cardiac	48,318 (45)	14,856 (41)	33,462 (47)
Surgical – cardiac	6049 (6)	2383 (7)	3666 (5)
Surgical – non-cardiac[b]	11,315 (10)	3414 (9)	7901 (11)
Trauma	1832 (2)	779 (2)	1053 (1)
Pre-existing Conditions[c] – no. (%)			
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)
Non-cardiac			
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/hematologic malignancy	13,572 (13)	4226 (12)	9346 (13)
Hypotension/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/electrolyte abnormality	15,696 (15)	5223 (14)	10,473 (15)
Septicemia	14,516 (13)	5204 (14)	9312 (13)
Acute CNS non-stroke 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)
Hospital Characteristics - no. (%)			
Bed size			
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)
Non-teaching	37,616 (35)	12,278 (34)	25,338 (35)
Ownership			
Military	2218 (2)	774 (2)	1444 (2)
Non-Profit	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			
North-East	15,190 (14)	5214 (14)	9976 (14)
South-East	32,372 (30)	10,592 (29)	21,780 (30)
Mid-West	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)
Year of the arrest – no. (%)			
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 arrest – no. (%)			
Non-invasive assisted ventilation	11,117 (10)	8164 (22)	2953 (4)
Dialysis[d]	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[e]	16,056 (15)	7822 (21)	8234 (12)
Antiarrhythmic agents[f]	3348 (3)	1641 (5)	1707 (2)
Arrest characteristics – no. (%)			
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 area	6471 (6)	2289 (6)	4182 (6)
Other[g]	2632 (2)	748 (2)	1882 (3)
Time of day			
Day (7:00am – 10:59pm)	72,547 (67)	24,853 (68)	47,694 (67)
Night (11:00pm – 6:59am)	35,532 (33)	11,611 (32)	23,921 (33)
Weekend			

Weekday (Monday 7am – Friday 11pm)	74,578 (69)	25,209 (69)	49,369 (69)
Weekend (Friday 11pm to Monday 7am)	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			
0 minutes	98,949 (92)	33,648 (92)	65,301 (91)
1 minutes	4819 (4)	1559 (4)	3260 (5)
≥ 2 minute	4311 (4)	1257 (3)	3054 (4)
Epinephrine administration – no. (%)	96,046 (89)	27,737 (76)	68,309 (95)
Time to epinephrine – median min (quartiles)	2 (0, 5)	1 (0, 4)	2 (1, 5)
Defibrillation[h] – no. (%)	17,479 (90)	8019 (89)	9460 (91)
Time to defibrillation - median min (quartiles)	1 (0, 3)	1 (0, 2)	2 (0, 4)

[a] CNS: central nervous system, OR: operating room, PACU: post-anesthesia care unit,

[b] Includes patients with an admission type of "obstetric" (n = 135)

[c] See eTable 1 in the Supplemental Material for definitions of pre-existing conditions

[d] Hemo- or peritoneal dialysis, continuous arteriovenous, or veno-venous hemofiltration/dialysis

[e] Dobutamine, dopamine (> 3 mcg/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/outpatient areas, delivery suite, rehabilitation/skilled nursing/mental health facilities, same day surgical areas, and "other"

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

Table 2. Patient, Hospital, and Event Characteristics in the Matched Cohort[a]			
	No intubation ≤ 15 min (n = 43,314)	**Intubation ≤ 15 min (n = 43,314)**	**Standardized difference**
Demographics			
Age – median years (quartiles)	70 (58, 79)	70 (58, 80)	0.014
Sex – no. (%)			
Male	25,332 (58)	25,486 (59)	0.007
Female	17,982 (42)	17,828 (41)	0.007
Race – no. (%)			
White	30,547 (71)	30,713 (71)	0.008
Black	8837 (20)	8710 (20)	0.007
Other	1361 (3)	1321 (3)	0.005
Not reported	2569 (6)	2570 (6)	< 0.001
Illness Category – no. (%)			
Medical – cardiac	15,779 (36)	15,716 (36)	0.003
Medical – non-cardiac	19,979 (46)	20,017 (46)	0.002
Surgical – cardiac	2274 (5)	2197 (5)	0.008
Surgical – non-cardiac[b]	4623 (11)	4708 (11)	0.006
Trauma	659 (2)	676 (2)	0.003
Pre-existing Conditions[c] – no. (%)			
Cardiac			
History of myocardial infarction	7477 (17)	7370 (17)	0.007
Myocardial infarction this admission	6786 (16)	6697 (15)	0.006
History of heart failure	10,186 (24)	10,170 (23)	0.001
Heart failure this admission	7852 (18)	7947 (18)	0.006
Non-cardiac			
Respiratory insufficiency	14,822 (34)	14,845 (34)	0.001
Diabetes mellitus	14,264 (33)	14,334 (33)	0.003
Renal insufficiency	14,893 (34)	14,739 (34)	0.007
Metastatic/hematologic malignancy	5579 (13)	5663 (13)	0.006
Hypotension/hypoperfusion	8659 (20)	8741 (20)	0.005
Pneumonia	5381 (12)	5351 (12)	0.002
Baseline depression in CNS function	4629 (11)	4636 (11)	0.001
Metabolic/electrolyte abnormality	6300 (15)	6306 (15)	< 0.001
Septicemia	5598 (13)	5707 (13)	0.007
Acute CNS non-stroke event	2708 (6)	2756 (6)	0.005
Hepatic insufficiency	2837 (7)	2841 (7)	< 0.001
Acute stroke	1639 (4)	1652 (4)	0.002
Major trauma	962 (2)	954 (2)	0.001
Hospital Characteristics - no. (%)			
Bed size			
1 – 249	8132 (19)	8016 (19)	0.007
250 – 499	17,367 (40)	17,444 (40)	0.004
500+	17,815 (41)	17,854 (41)	0.002
Teaching Status			

Major	14,747 (34)	14,609 (34)	0.007
Minor	13,252 (31)	13,357 (31)	0.005
Non-teaching	15,315 (35)	15,348 (35)	0.002
Ownership			
Military	905 (2)	928 (2)	0.004
Non-Profit	31,189 (72)	31,195 (72)	< 0.001
Government	6444 (15)	6385 (15)	0.004
Private	4776 (11)	4806 (11)	0.002
Location			
Rural	2342 (5)	2348 (5)	0.001
Urban	40,972 (95)	40,966 (95)	0.001
Geographical Location			
North-East	6032 (14)	6077 (14)	0.003
South-East	13,184 (30)	13,123 (30)	0.003
Mid-West	9090 (21)	9160 (21)	0.004
South-Central	8977 (21)	8898 (21)	0.005
West	6031 (14)	6056 (14)	0.002
Year of the arrest – no. (%)			
2000 – 2002	4319 (10)	4480 (10)	0.012
2003 – 2004	6783 (16)	6642 (15)	0.009
2005 – 2006	6691 (15)	6824 (16)	0.008
2007 – 2008	6484 (15)	6486 (15)	< 0.001
2009 – 2010	5837 (13)	5709 (13)	0.009
2011 – 2012	5965 (14)	6030 (14)	0.004
2013 – 2014	7235 (17)	7143 (16)	0.006
In place at time of arrest – no. (%)			
Non-invasive assisted ventilation	2296 (5)	2377 (5)	0.008
Dialysis[d]	1185 (3)	1176 (3)	0.001
Implantable cardiac defibrillator	827 (2)	780 (2)	0.008
Intra-arterial catheter	1455 (3)	1417 (3)	0.005
Electrocardiogram	31,224 (72)	31,059 (72)	0.008
Pulse oximeter	23,623 (55)	23,524 (54)	0.005
Vasoactive agents[e]	5430 (13)	5426 (13)	< 0.001
Antiarrhythmic agents[f]	1123 (3)	1093 (3)	0.004
Arrest characteristics – no. (%)			
Location			
Emergency department	4422 (10)	4546 (11)	0.009
Floor with telemetry	9342 (22)	9373 (22)	0.002
Floor without telemetry	12,263 (28)	12,331 (28)	0.003
Intensive care unit	13,556 (31)	13,384 (31)	0.009
OR, PACU, or interventional area	2585 (6)	2550 (6)	0.003
Other[g]	1146 (3)	1130 (3)	0.002
Time of day			
Day (7:00am – 10:59pm)	28,953 (67)	28,878 (67)	0.004
Night (11:00pm – 6:59am)	14,361 (33)	14,436 (33)	0.004
Weekend			

Weekday (Monday 7am – Friday 11pm)	29,809 (69)	28,886 (69)	0.004
Weekend (Friday 11pm to Monday 7am)	13,505 (31)	13,428 (31)	0.004
Hospital wide cardiac arrest response activated	36,562 (84)	36,529 (84)	0.002
Witnessed	32,884 (76)	32,835 (76)	0.003
First documented pulseless rhythm			
Asystole	16,324 (38)	16,574 (38)	0.012
Pulseless electrical activity	20,344 (47)	20,065 (46)	0.013
Ventricular fibrillation	4478 (10)	4501 (10)	0.002
Pulseless ventricular tachycardia	2168 (5)	2174 (5)	0.001
Time to compressions			
0 minutes	39,465 (91)	39,537 (91)	0.006
1 minute	1963 (5)	1931 (4)	0.004
≥ 2 minutes	1886 (4)	1846 (4)	0.005
Epinephrine before matching – no. (%)	23,084 (53)	23,226 (54)	0.007
Time to epinephrine – median min (quartiles)	1 (1, 3)	1 (1, 3)	0.027
Defibrillation before matching[h] – no. (%)	3895 (59)	3859 (58)	0.016
Time to defibrillation - median min (quartiles)	1 (0, 2)	1 (0, 2)	0.050

[a] CNS: central nervous system, OR: operating room, PACU: post-anesthesia care unit,

[b] Includes patients with an admission type of "obstetric" (n = 110)

[c] See eTable 1 in the Supplemental Material for definitions of pre-existing conditions

[d] Hemo- or peritoneal dialysis, continuous arteriovenous, or veno-venous hemofiltration/dialysis

[e] Dobutamine, dopamine (> 3 mcg/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/outpatient areas, delivery suite, rehabilitation/skilled nursing/mental health facilities, same day surgical areas, and "other"

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

Table 3. Outcomes in the overall and time-dependent propensity score matched cohort[a]						
	Unadjusted analysis			**Propensity score matched analysis**		
	Not intubated[b]	**Intubated[b]**	**Risk ratio (95%CI)**	**Not intubated[b]**	**Intubated[b]**	**Risk ratio (95%CI)**
ROSC	42,366/71,611 (59.2)	25,174/36,461 (69.0)	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	12,140/71,615 (17.0)	12,116/36,464 (33.2)	0.58 (0.57, 0.59)	8407/43,314 (19.4)	7052/43,314 (16.3)	0.84 (0.81, 0.87)
Favorable functional outcomes[c]	7717/69,212 (11.2)	8787/34,236 (25.7)	0.55 (0.54, 0.56)	5672/41,733 (13.6)	4439/41,868 (10.6)	0.78 (0.75, 0.81)

[a] ROSC indicates return of spontaneous circulation, 95%CI indicates 95% confidence intervals

[b] Results are provided as number of patients with the outcomes/total number of patients (proportion with the outcome)

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

FIGURE LEGENDS

Figure 1. Inclusion and exclusion criteria

Out of 263,832 cardiac arrests in the database, 143,810 met the inclusion criteria for the current study and 108,079 patients were included in the primary cohort.

IHCA denotes in-hospital cardiac arrest

Figure 2. Forest plot of subgroup analyses in the propensity matched cohort

Risk ratios with 95% confidence intervals for predefined subgroup analyses. The p-value represents the "Type 3" p-value for the interaction between intubation and a given subgroup. The dashed vertical line on the left represents the risk ratio in the overall cohort and the dashed line on the right represents a risk ratio of one (i.e. no effect). Except for the time of the matching, there were significant differences according to all other subgroups. Survival to hospital discharge is presented as patients with the outcome/total patients (proportion).

OR denotes operating room and PACU post-anesthesia care unit

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