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Clinical paper

Guideline removal of atropine and survival after adult in-hospital cardiac arrest with a non-shockable rhythm

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Abstract

Aim: To determine whether the removal of atropine from the 2010 ACLS guidelines for non-shockable cardiac arrests was associated with a change in survival.

Methods: Using the Get With The Guidelines®-Resuscitation registry, we included adults with an index in-hospital cardiac arrest between 2006 and 2015. The primary outcome was survival to hospital discharge. Secondary outcomes included return of spontaneous circulation and favorable functional outcome. An interrupted time-series analysis was used to compare survival before (pre-guidelines) and after (post-guidelines) introduction of the 2010 guidelines. A difference-in-difference approach was used to compare the interrupted time-series results between the non-shockable and shockable cohorts to account for guideline changes unrelated to atropine.

Results: We included 20,499 non-shockable and 3968 shockable cardiac arrests. Patient characteristics were similar between the pre-guidelines and post-guidelines period. Atropine was used for 8653 (87%) non-shockable and 680 (35%) shockable cardiac arrests in the pre-guidelines period and 3643 (35%) non-shockable and 320 (16%) shockable cardiac arrests in the post-guidelines period. The change over time in survival from the pre-guidelines to the post-guidelines period was not significantly different for the non-shockable compared to the shockable cohort (risk difference: 2.0% [95%CI: −0.8, 4.8] per year, p = 0.17). The immediate change in survival after introducing the guidelines was also not different between the cohorts (risk difference: 3.5% [95%CI: −2.6, 9.7], p = 0.26). Results were similar for the secondary outcomes and in multiple sensitivity analyses.

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Conclusions: The removal of atropine from the 2010 guidelines was not associated with a significant change in survival.
Keywords: Heart arrest, Atropine, Guideline, Advanced cardiac life support, American heart association, Interrupted time series analysis

Introduction

Atropine was removed from the 2010 American Heart Association's Advanced Cardiac Life Support (ACLS) guidelines as standard treatment for cardiac arrest patients with a non-shockable rhythm.[1] The available literature for atropine administration in non-shockable rhythms is conflicting and has largely been limited to studies with low-quality of evidence,[1] including one small non-randomized clinical trial,[2] observational studies,[3–9] and case series.[10–12]

The majority of updates to the 2010 ACLS guidelines were applicable to all cardiac arrest patients independent of the underlying rhythm (e.g., emphasis on high-quality cardiopulmonary resuscitation [CPR] and post-cardiac arrest care).[1] However, the removal of atropine from the guidelines was specific to patients with a non-shockable rhythm.[1] Using data from an in-hospital cardiac arrest registry, Moskowitz et al. found that atropine administration rates rapidly decreased in the United States following implementation of the 2010 ACLS guidelines.[13] These findings provide a platform on which to examine survival in relation to the removal of atropine as standard treatment for patients with a non-shockable rhythm.

The goal of this investigation was to evaluate whether the 2010 ACLS guideline removal of atropine was associated with a change in survival for adult in-hospital cardiac arrest patients with a non-shockable rhythm.

Methods

Study design and data source

This was an observational study using data from the Get With The Guidelines-Resuscitation (GWTG-R) registry. The GWTG-R is a prospective, quality-improvement registry of in-hospital cardiac arrest in the United States, administered by the American Heart Association. The design and data collection process of the registry have been described in detail elsewhere.[14–16] Cardiac arrest is defined as a loss of pulse requiring chest compression, defibrillation or both, with a hospital-wide or unit-based emergency response by acute care personnel. Hospital-level data were obtained from the 2010 and 2013 American Hospital Association data sets.[17] All participating hospitals are required to comply with local regulatory guidelines.

Study population and outcomes

We included adult patients (≥18 years of age) between January 1, 2006 and December 31, 2015 with an index cardiac arrest and documented chest compressions ≥2 min. Hospital visitors and employees were not included. Patients with missing data on atropine use, survival, and covariates (Table 1) were excluded for the primary analysis. Patients with missing data were included after imputing the missing values in a preplanned sensitivity analysis (see Section "Statistical analysis").

Atropine use was defined as the administration of atropine at any time during the cardiac arrest. Timing and dose of atropine administration was not available in the GWTG-R registry. The primary outcome was survival to hospital discharge. The secondary outcomes were sustained return of spontaneous circulation (ROSC) and survival to hospital discharge with a favorable functional outcome. Sustained ROSC was defined as the presence of a pulse and no further need for chest compressions (including initiation of cardiopulmonary bypass or extracorporeal membrane oxygenation) for at least 20 min. Favorable functional outcome was defined as a Cerebral Performance Category (CPC) score of 1 (mild or no neurological deficit) or 2 (moderate cerebral disability) in line with the Utstein criteria.[18]

Statistical analysis

The goal of this analysis was to evaluate whether the 2010 ACLS guideline removal of atropine was associated with a change in survival for patients with a non-shockable (asystole or pulseless electrical activity) in-hospital cardiac arrest. In brief, since survival has been improving over time for adult in-hospital cardiac arrest patients,[19] we performed an interrupted time-series analysis to compare survival trends before and after implementation of the 2010 guidelines. To account for potential changes in survival unrelated to the specific guideline removal of atropine, we used a difference-in-difference approach to compare changes in survival for patients with an initial non-shockable rhythm and a high propensity to receive atropine to patients with an initial shockable rhythm and a low propensity to receive atropine (serving as a comparison group).[20] Additional details on the interrupted time-series and difference-in-difference approach are provided below and in the Supplemental material (Supplemental methods, Figs. S1–S2).

The time before guideline implementation (referred to as "pre-guidelines") was defined as the time from implementation of the 2005 guidelines to publication of the 2010 guidelines (April 2006 to September 2010). The time after guideline implementation (referred to as "post-guidelines") was defined as the time from implementation of the 2010 guidelines to publication of the 2015 guidelines (April 2011 to September 2015). We defined an implementation period (October 2010 to March 2011) which was censored from the primary analysis. Time was categorized in quarters per year.

A substantial number of patients (53%) with an initial shockable rhythm received atropine (e.g., a shockable rhythm that becomes non-shockable prior to ROSC or termination of resuscitation) during the "pre-guidelines" period. In addition, some patients (20%) with an initial non-shockable rhythm did not receive atropine. To create two distinct cohorts, we calculated separate propensity scores for patients with a non-shockable rhythm and patients with a shockable rhythm, based on data in the "pre-guidelines" period, and applied the parameters to patients in the "post-guidelines" period. The propensity score model was developed using logistic regression with generalized estimating equations (GEE) to account for clustering of patients within hospitals. Atropine use was included as the dependent variable and patient, event, and predefined hospital characteristics were included as the independent variables (Table 1). The propensity score was stratified in quintiles to obtain two cohorts with distinct propensities to receive atropine. We

Table 1 – Patient, event, and hospital characteristics in the propensity score selected cohort.

	Non-shockable			Shockable		
	Pre-guidelines (n = 10,002)	Post-guidelines (n = 10,497)	SDD	Pre-guidelines (n = 1958)	Post-guidelines (n = 2010)	SDD
Demographics						
Sex						
Female	3468 (35)	3679 (35)	0.01	741 (38)	766 (38)	0.01
Male	6534 (65)	6818 (65)	–0.01	1217 (62)	1244 (62)	−0.01
Age, median (IQR), years	66 (53, 77)	65 (54, 76)	–0.02	65 (55, 76)	64 (55, 73)	–0.07
Race						
White	6140 (61)	6177 (59)	–0.05	1829 (93)	1895 (94)	0.04
Black	3505 (35)	4093 (39)	0.08	93 (5)	89 (4)	–0.02
Other	357 (4)	227 (2)	–0.08	36 (2)	26 (1)	–0.04
Illness category						
Medical						
Cardiac	2487 (25)	3133 (30)	0.11	1251 (64)	1288 (64)	0.00
Non-cardiac	6618 (66)	6492 (62)	–0.09	59 (3)	38 (2)	–0.07
Surgical						
Cardiac	5 (<1)	2 (<1)	–0.02	621 (32)	655 (33)	0.02
Non-cardiac[a]	720 (7)	641 (6)	–0.04	24 (1)	28 (1)	0.01
Trauma	172 (2)	229 (2)	0.03	3 (<1)	1 (<1)	–0.03
Pre-existing conditions[b]						
Cardiac						
Heart failure this admission	1692 (17)	1588 (15)	–0.05	369 (19)	343 (17)	–0.05
History of heart failure	1596 (16)	1833 (17)	0.04	422 (22)	502 (25)	0.08
Myocardial infarction this admission	1287 (13)	1414 (13)	0.02	891 (46)	832 (41)	–0.08
History of myocardial infarction	1198 (12)	1264 (12)	0.00	545 (28)	515 (26)	–0.05
Non-cardiac						
Respiratory insufficiency	4716 (47)	5534 (53)	0.11	446 (23)	418 (21)	–0.05
Diabetes mellitus	3219 (32)	3444 (33)	0.01	374 (19)	448 (22)	0.08
Renal insufficiency	3912 (39)	4238 (40)	0.03	282 (14)	302 (15)	0.02
Metastatic/hematologic malignancy	1933 (19)	1826 (17)	–0.05	35 (2)	34 (2)	–0.01
Hypotension	2634 (26)	2550 (24)	–0.05	249 (13)	171 (9)	–0.14
Pneumonia	1828 (18)	1989 (19)	0.02	96 (5)	104 (5)	0.01
Baseline depression in CNS function	1415 (14)	1099 (10)	–0.11	133 (7)	80 (4)	–0.12
Metabolic/electrolyte abnormality	2074 (21)	2607 (25)	0.10	142 (7)	130 (6)	–0.03
Septicemia	2116 (21)	2332 (22)	0.03	70 (4)	58 (3)	–0.04
Acute CNS non-stroke event	711 (7)	771 (7)	0.01	70 (4)	64 (3)	–0.02
Hepatic insufficiency	1231 (12)	1284 (12)	0.00	64 (3)	51 (3)	–0.04
Acute stroke	413 (4)	423 (4)	–0.01	64 (3)	54 (3)	–0.03
Major trauma	188 (2)	251 (2)	0.04	26 (1)	26 (1)	0.00
Arrest Characteristics						
In place at time of arrest						
Antiarrhythmic agents[c]	294 (3)	189 (2)	–0.07	676 (35)	452 (22)	–0.27
Mechanical ventilation	2779 (28)	3126 (30)	0.04	727 (37)	632 (31)	–0.12
Vasoactive agents[d]	1779 (18)	1342 (13)	–0.14	565 (29)	482 (24)	–0.11
Intra-arterial catheter	218 (2)	281 (3)	0.03	477 (24)	462 (23)	–0.03
Implantable defibrillator	32 (<1)	34 (<1)	0.00	70 (4)	80 (4)	0.02
Dialysis[e]	354 (4)	262 (3)	–0.06	35 (2)	29 (1)	–0.03
Pulse oximeter	6005 (60)	6832 (65)	0.10	1650 (84)	1714 (85)	0.03
Electrocardiogram	7508 (75)	8174 (78)	0.07	1941 (99)	1953 (97)	–0.15
Location						
Emergency Department	588 (6)	725 (7)	0.04	238 (12)	242 (12)	0.00
Intensive care unit	4703 (47)	5280 (50)	0.07	1279 (65)	1281 (64)	–0.03
Floor						
With telemetry	1746 (17)	1847 (18)	0.00	303 (15)	326 (16)	–0.02
Without telemetry	2834 (28)	2550 (24)	–0.09	47 (2)	42 (2)	0.02
Other[f]	131 (1)	95 (1)	–0.04	91 (5)	119 (6)	0.06

(continued on next page)

Table 1 *(continued)*

	Non-shockable			Shockable		
	Pre-guidelines (n = 10,002)	Post-guidelines (n = 10,497)	SDD	Pre-guidelines (n = 1958)	Post-guidelines (n = 2010)	SDD
Time of day[g]						
Day	3841 (38)	3847 (37)	–0.04	1524 (78)	1637 (81)	0.09
Night	6161 (62)	6650 (63)	0.04	434 (22)	373 (19)	–0.09
Day of week[h]						
Weekday	6390 (64)	6706 (64)	0.00	1464 (75)	1509 (75)	0.01
Weekend	3612 (36)	3791 (36)	0.00	494 (25)	501 (25)	–0.01
Witnessed	6604 (66)	7461 (71)	0.11	1862 (95)	1932 (96)	0.05
Initial rhythm						
Asystole	8005 (80)	7971 (76)	–0.10	–	–	–
Pulseless electrical activity	1997 (20)	2526 (24)	0.10	–	–	–
Ventricular fibrillation	–	–	–	1078 (55)	1016 (51)	0.09
Pulseless ventricular tachycardia	–	–	–	880 (45)	994 (49)	–0.09
Hospital characteristics						
Number of beds						
1– 249	1622 (16)	1065 (10)	–0.18	323 (17)	417 (21)	0.11
250– 499	4078 (41)	4903 (47)	0.12	649 (33)	675 (34)	0.01
>500	4302 (43)	4529 (43)	0.00	986 (50)	918 (46)	–0.09
Teaching status						
Major	3712 (37)	4627 (44)	0.14	790 (40)	870 (43)	0.06
Minor	3187 (32)	3501 (33)	0.03	517 (26)	594 (30)	0.07
Non-teaching	3103 (31)	2369 (23)	–0.19	651 (33)	546 (27)	–0.13
Ownership						
Military	528 (5)	194 (2)	–0.19	34 (2)	40 (2)	0.02
Nonprofit	4749 (47)	5863 (56)	0.17	1680 (86)	1674 (83)	–0.07
Government	2041 (20)	2503 (24)	0.08	114 (6)	174 (9)	0.11
Private	2684 (27)	1937 (18)	–0.20	130 (7)	122 (6)	–0.02
Location						
Rural	150 (2)	156 (1)	0.00	71 (4)	83 (4)	0.03
Urban	9852 (99)	10,341 (99)	0.00	1887 (96)	1927 (96)	–0.03
Geographical location						
North-East	1127 (11)	2002 (19)	0.22	233 (12)	215 (11)	–0.03
South-East	3923 (39)	3535 (34)	–0.12	370 (19)	304 (15)	–0.10
Mid-West	688 (7)	647 (6)	–0.03	629 (32)	717 (36)	0.07
South-Central	4174 (42)	4217 (40)	–0.03	140 (7)	177 (9)	0.06
West	90 (1)	96 (1)	0.00	586 (30)	597 (30)	0.00

SDD denotes standardized difference, IQR denotes interquartile range, CNS denotes central nervous system. Categorical data are presented as counts with frequencies. Continuous data are presented as medians with interquartile range.

[a] Includes patients with an obstetric admission.

[b] Definitions are provided in the Supplemental Material.

[c] Continuous infusion of amiodarone, lidocaine, procainamide, or other antiarrhythmic(s).

[d] Continuous infusion of dobutamine, dopamine >3 mcg/kg/min, epinephrine, nitroglycerin, norepinephrine, phenylephrine, vasopressin, or other vasoactive agent(s).

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

[f] Ambulatory and outpatient areas, delivery suite, rehabilitation facility, skilled nursing facility, mental health facility, same-day surgical area, operating room, post-anesthesia recovery room, or interventional unit.

[g] Day refers to 7:00 am to 10:59 pm, Night refers to 11:00 pm to 6:59 am.

[h] Weekday refers to Monday 7:00 am to Friday 10:59 pm, Weekend refers to Friday 11:00 pm to Monday 6:59 am.

isolated non-shockable cardiac arrests in the fifth quintile (high propensity to receive atropine) and shockable cardiac arrests in the first quintile (low propensity to receive atropine). Variable definitions and additional details are provided in the Supplemental material (Supplemental methods, Figs. S3–S5, and Table S1).

Using the two cohorts (non-shockable vs. shockable) identified in the propensity score analysis, we developed a generalized linear model with GEE to estimate the change in slope (i.e., survival trend) from the "pre-guidelines" to "post-guidelines" period and the change in level (i.e., abrupt survival change) during the implementation period. We then calculated the difference for the change in slope and level for the non-shockable cohort compared to the shockable cohort by adding interaction terms to the GEE model. A positive difference indicated a harmful effect of atropine removal and a negative difference indicated a beneficial effect of atropine removal.

We conducted three preplanned sensitivity analyses. First, we performed modified Poisson regression to obtain relative risk estimates for the primary outcome. Second, missing data were

imputed using the fully conditional specification method assuming that the data were "missing at random".[21] Additional details are provided in the Supplemental material (Supplemental methods, Table S2). Third, to account for various periods of guideline implementation, we repeated the primary analysis without the censored implementation period and with the implementation period defined as the time from October 2010 to September 2011. We also conducted two post-hoc analyses by repeating the primary analysis without the propensity score analysis and after stratifying the propensity score in tertiles (rather than quintiles).

All analyses were two-sided, with a significance level of $p < 0.05$. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Patient characteristics

The propensity score analysis identified 24,467 patients, of which 20,499 patients were included in the non-shockable cohort and 3968 patients were included in the shockable cohort (Fig. 1). The median age was 65 (quartiles: 54, 77) years and 35% of patients were female in the non-shockable cohort, while the median age was 65 (quartiles: 55, 74) years and 38% of patients were female in the shockable cohort. Baseline characteristics of each cohort were comparable between the pre-guidelines and post-guidelines period (Table 1). Atropine was provided to 8653 (87%) non-shockable and 680 (35%) shockable cardiac arrests in the pre-guidelines period and 3643 (35%) non-shockable and 320 (16%) shockable cardiac arrests in the post-guidelines period (Fig. S3).

Primary outcome

For the non-shockable cohort, the survival rate increased by 0.8% (95%CI: 0.3, 1.3, $p < 0.01$) per year in the pre-guidelines period and by 0.2% (95%CI: −0.4, 0.8, $p = 0.56$) per year in the post-guidelines period (risk difference: −0.6% [95%CI: −1.4, 0.2] per year, $p = 0.14$). The immediate change in survival after introducing the guidelines was 1.2% (95%CI: −0.9, 3.3, $p = 0.27$).

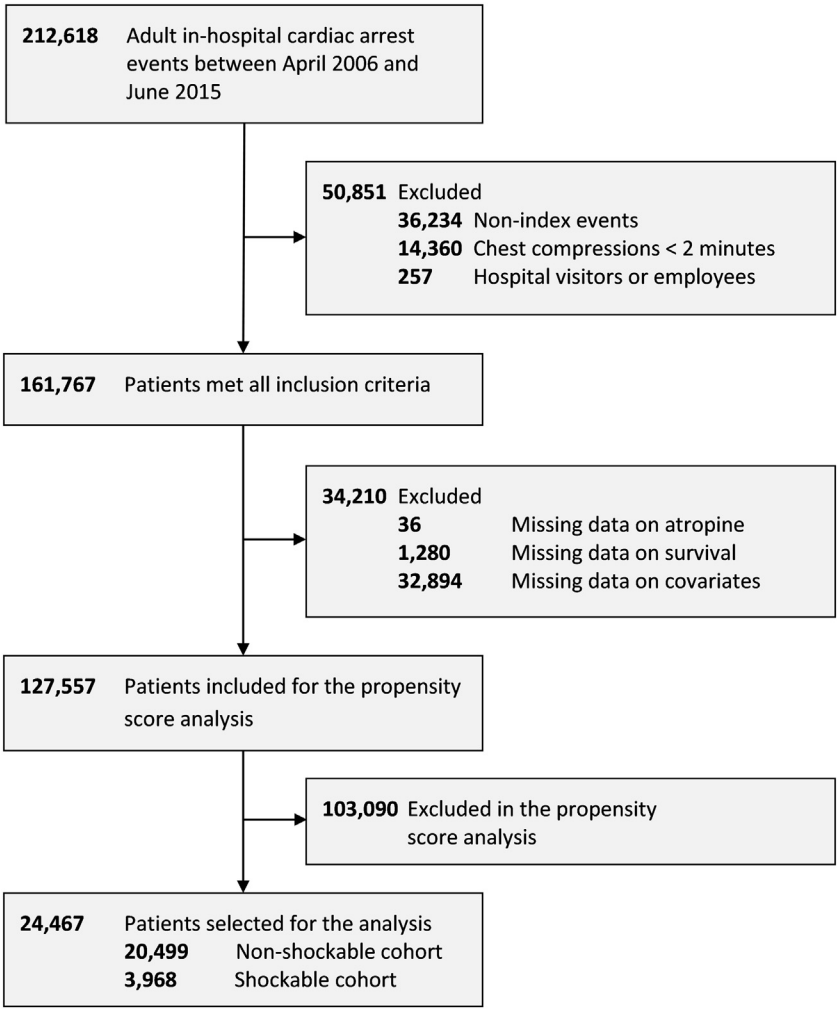

Fig. 1 – Flow diagram of included patients.
Between April 2006 and June 2015, 212,618 cardiac arrest events were registered in the Get With The Guidelines-Resuscitation registry. 127,557 patients were included for the propensity score analysis, of which 24,467 were selected for the primary analysis.

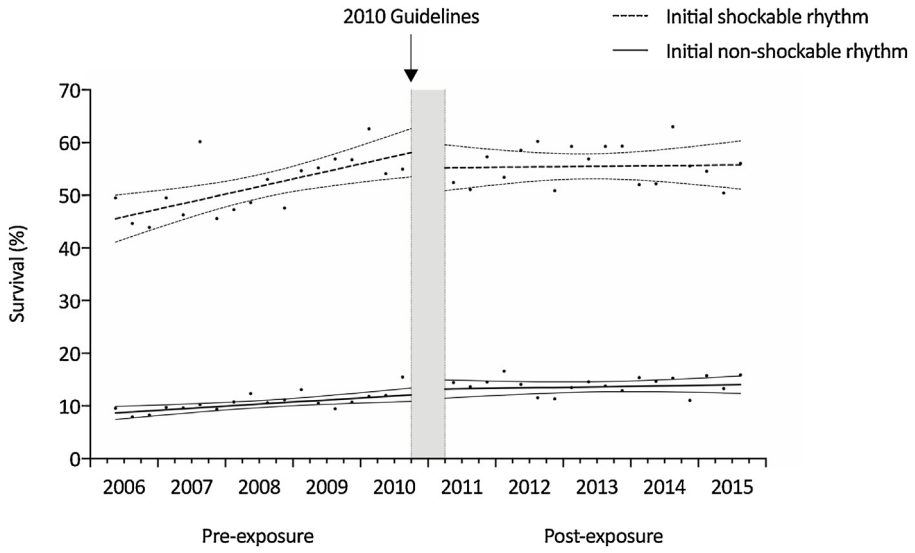

Fig. 2 – Interrupted time-series for survival to hospital discharge.
The solid dots represent the percent survival per annual quarter. Lines represent the estimated change over time in survival with 95% confidence intervals. The shaded area represents the implementation period (October 2010 to March 2011). The slope change in survival from the pre-guidelines to the post-guidelines period was not significantly different for the non-shockable (solid lines) compared to the shockable (dashed lines) cohort (risk difference: 2.0% [95%CI: (−0.8, 4.8] per year, p = 0.17). The level change in survival was also not different between the cohorts (risk difference: 3.5% [95%CI: (−2.6, 9.7], p = 0.26).

For the shockable cohort, the survival rate increased by 2.9% (95% CI: 1.1, 4.7, p < 0.01) per year in the pre-guidelines period and by 0.1% (95%CI: −1.6, 1.9, p = 0.89) per year in the post-guidelines period (risk difference: −2.7% [95%CI: −5.3, −0.2] per year, p = 0.04). The immediate change in survival after introducing the guidelines was −2.5% (95%CI: −8.4, 3.3, p = 0.40).

The change over time in survival from the pre-guidelines to the post-guidelines period was not significantly different for the non-shockable compared to the shockable cohort (risk difference: 2.0% [95%CI: −0.8, 4.8] per year, p = 0.17). The immediate change in survival after introducing the guidelines was also not significantly different for the two cohorts (risk difference: 3.5% [95%CI: −2.6, 9.7], p = 0.26). The sensitivity analysis to obtain relative risk estimates yielded similar results as the primary analysis. Additional details are provided in Fig. 2 and Table 2.

Table 2 – Interrupted time-series models for survival to hospital discharge.

	Absolute risk (95%CI)	P-value	Relative risk (95%CI)	P-value
Non-shockable cohort (n = 20,499)				
Pre-slope	0.8 (0.3, 1.3)	<0.01	1.08 (1.03, 1.13)	<0.01
Post-slope	0.2 (–0.4, 0.8)	0.56	1.01 (0.97, 1.06)	0.56
Level change	1.2 (–0.9, 3.3)	0.27	1.09 (0.92, 1.28)	0.31
Pre-post slope change	–0.6 (–1.4, 0.2)	0.14	0.94 (0.88, 1.00)	0.07
Shockable cohort (n = 3968)				
Pre-slope	2.9 (1.1, 4.7)	<0.01	1.06 (1.02, 1.10)	<0.01
Post-slope	0.1 (–1.6, 1.9)	0.89	1.00 (0.97, 1.03)	0.89
Level change	–2.5 (–8.4, 3.3)	0.40	0.95 (0.86, 1.06)	0.40
Pre-post slope change	–2.7 (–5.3, –0.2)	0.04	0.95 (0.90, 0.99)	0.03
Difference-in-difference				
Level difference	3.5 (–2.6, 9.7)	0.26	1.14 (0.94, 1.39)	0.18
Pre-post slope difference	2.0 (–0.8, 4.8)	0.17	0.99 (0.91, 1.07)	0.76

Pre-slope refers to the annual change over time in survival for the pre-guidelines period, post-slope refers to the annual change over time in survival for the post-guidelines period, level difference refers to the immediate change in survival after introducing the guidelines, pre-post slope difference refers to the difference in slope from the pre-guidelines to post-guidelines period.

Secondary outcomes

For the analysis on ROSC, we included 20,629 patients in the non-shockable cohort and 3995 patients in the shockable cohort. The change over time in ROSC from the pre-guidelines to the post-guidelines period was not significantly different for the non-shockable compared to the shockable cohort (risk difference: 1.0% [95%CI: −1.4, 3.3] per year, p = 0.43). The immediate change in ROSC between the pre-guidelines and post-guidelines period was also not significantly different for the two cohorts (risk difference: 1.0% [95%CI: −5.0, 6.9], p = 0.75).

For the analysis on favorable functional outcome, we included 19,738 patients in the non-shockable cohort and 3684 patients in the shockable cohort. The change over time in favorable functional outcome from the pre-guidelines to the post-guidelines period was not significantly different for the non-shockable compared to the shockable cohort (risk difference: 0.3% [95%CI: −2.8, 3.3] per year, p = 0.87). The immediate change in favorable functional outcome between the pre-guidelines and post-guidelines period was also not significantly different for the two cohorts (risk difference: 5.0% [95%CI: −1.6, 11.5], p = 0.14). Additional details are provided in the Supplemental material (Figs. S6–S7 and Tables S3–S4).

Sensitivity analyses

Data were missing on at least one variable in 34,210 (21%) patients. A total of 161,767 patients were included for the multiple imputation analysis. Between 26,955 and 26,981 patients with a non-shockable rhythm and between 5372 and 5397 patients with a shockable rhythm were isolated in the propensity score analyses across the 20 imputed data sets. The results of these analyses were similar to the primary analysis (risk difference in slope: 1.1% [95%CI: −1.5, 3.7], p = 0.41 per year; risk difference in level: 2.3% [95%CI: −3.7, 8.3], p = 0.45).

In the sensitivity analyses accounting for different time-periods of guideline implementation, there was no difference in survival between the non-shockable (n = 21,349) and the shockable (n = 4162) cohort when excluding the implementation period (risk difference in slope: 1.9% [95%CI: −0.7, 4.6], p = 0.16 per year; risk difference in level: 2.8% [95%CI: −3.6, 9.2], p = 0.40). There was also no difference in survival between the non-shockable (n = 19,718) and shockable (n = 3770) cohort when considering a one-year implementation period (risk difference in slope: 2.8% [95%CI: 0.0, 5.7] per year, p = 0.05; risk difference in level: 1.7% [95%CI: −5.4, 8.8], p = 0.64). Additional details are provided in the Supplemental material (Table S5).

Post-hoc analyses

For the two post-hoc analyses, the difference in survival between the non-shockable (n = 102,259) and shockable (n = 19,911) cohort remained non-significant without the propensity score analysis (risk difference in slope: 0.7% [95%CI: −0.4, 1.9] per year, p = 0.22; risk difference in level: 1.8% [95%CI: −1.2, 4.8], p = 0.25). The difference in survival between the non-shockable (n = 34,120) and shockable (n = 6637) cohort was also non-significant when stratifying the propensity score by tertiles (risk difference in slope: 0.6% [95%CI: −1.6, 2.8] per year, p = 0.60; risk difference in level: 2.1% [95%CI: −3.1, 7.3], p = 0.42). Additional details are provided in the Supplemental material (Table S6).

Discussion

In this multicenter, observational study, the removal of atropine from the 2010 ACLS guidelines was not associated with a change in survival for non-shockable in-hospital cardiac arrests. The removal of atropine from the guidelines was also not associated with a change in ROSC or favorable neurological outcome. Our findings remained consistent across multiple sensitivity analyses.

There is a scarcity of studies comparing the use of atropine to no atropine in adult in-hospital cardiac arrest patients with a non-shockable rhythm.[1] A small non-randomized clinical trial (n = 21) from 1981 found no difference in mortality between out-of-hospital cardiac arrest patients receiving atropine and those not receiving atropine.[2] An observational study (n = 4662) from 2001 found the use of atropine in out-of-hospital cardiac arrest to be negatively associated with ROSC,[7] similar to the results from two smaller observational studies in in-hospital cardiac arrest.[3,6] By comparison, two observational studies from 1984 (n = 170) and 1994 (n = 529) including out-of-hospital cardiac arrests found atropine use to be associated with higher initial survival.[8,9] The remainder of studies on the use of atropine are largely limited to case reports and no randomized trials have examined the use of atropine in non-shockable cardiac arrest.[10–12] Although longer duration of cardiac arrest has been associated with poor survival, none of the previous studies accounted for the time to atropine and only few studies accounted for other potential confounding variables, a practice which is likely to introduce bias.[22]

Directly comparing the use of atropine to no use of atropine could introduce "resuscitation-time bias", i.e. the issue that the use of atropine is likely related to the length of cardiac arrest, which in turn has been associated with poor outcomes.[22] Methods to handle "resuscitation time-bias" have been described elsewhere,[22–24] but are dependent on the timing of the intervention, which is rarely available in larger cardiac arrest registries (including GWTG-R). As timing of atropine delivery was not available in the GWTG-R registry, we were unable to use these approaches. The use of interrupted time-series can mitigate this and other potential biases, assuming that unmeasured confounders are invariant across years. For instance, the length of cardiac arrest and the timing when patients would be eligible to receive atropine are likely not different before and after introducing the guidelines. In addition, the use of a difference-in-difference approach accounts for unmeasured confounders that changes with time by assuming these are invariant across groups. Additional details on this approach are provided in the Supplemental material (Supplemental methods, Figs. S1–S2).

Our primary finding supports the removal of atropine as routine management for adult in-hospital cardiac arrest patients with a non-shockable rhythm. We found that the decrease in survival from the "pre-guidelines" period to the "post-guidelines" period was smaller for non-shockable cardiac arrests (for whom atropine was removed) compared to shockable cardiac arrests (comparison group), which indicates that the removal of atropine had a beneficial effect on survival, although the difference in results between the two cohorts was non-significant. In theory, atropine reverses the cholin ergic-mediated decreased heart rate and decreased conduction in the sinoatrial and atrioventricular node.[25] This response may be useful to counteract bradycardia in the presence of hypotension,[26] although the effect is uncertain in cardiac arrest, particularly when given in concert with epinephrine. While we did not find any significant evidence that the removal of atropine from the guidelines was detrimental, we believe post-guideline outcome

monitoring, similar to post-marketing drug surveillance,[27] is a critical aspect of clinical guideline development and implementation.

The implementation period for the primary analysis was determined based on visual inspection of quarterly atropine administration rates, suggesting a rapid decrease in atropine use within the first six months after publication of the 2010 guidelines.[13] However, the implementation of guidelines is often delayed, and medical-care may not always adhere to evidence-based guidelines.[28,29] For instance, previous studies from the United States and Europe suggest that only 30–40% of hospitals implemented targeted temperature management within 1–2 years following guideline publication.[30–32] Another study from Canada assessed the pre-hospital implementation of the 2005 American Heart Association guidelines and found a median time to implementation of 415 days,[33] similar to what has been reported in the Netherlands.[34] In the current study, the difference in survival between the non-shockable and shockable cohort remained non-significant when considering a one-year implementation period as a sensitivity analysis. However, while we found a gradual increase in survival prior to publication of the guidelines, there was a decrease in survival over time for shockable cardiac arrests after 2010 (Table 2, Table S5). This finding was unexpected and warrants further exploration in future investigations.

Our study should be interpreted in the context of the model assumptions and the following limitations. First, for the primary analysis, we assumed that the survival trends followed a linear pattern. Second, we assumed that no other intervention only targeting shockable rhythms or non-shockable rhythms was implemented near the same time as the 2010 guidelines. This also assumes that adherence to the 2010 guidelines did not differ for non-shockable and shockable cardiac arrests. Third, we assumed that the survival trend for patients with a non-shockable rhythm would have changed similar to patients with a shockable rhythm in the absence of the guideline removal of atropine. Fourth, despite its advantages, the difference-in-difference approach provides results with relatively large confidence intervals. As such, we might have been underpowered to detect small, but clinically relevant differences in outcomes between the groups. Lastly, although we attempted to create two distinct cohorts (non-shockable cardiac arrests with high propensity and shockable cardiac arrests with low propensity to receive atropine), there was some overlap in regard to atropine use, which may have diluted any difference in survival between the non-shockable cohort and shockable cohort. The propensity score analysis also reduced the number of patients eligible for the analysis, thus resulting in relatively wide confidence intervals, particularly for the shockable cohort. To partly account for this limitation, we conducted separate sensitivity analyses using the full cohort and dividing the cohort into tertiles.

Conclusions

The removal of atropine from the 2010 American Heart Association's ACLS guidelines was not associated with a change in survival to hospital discharge. These findings support the removal of atropine from the 2010 guidelines. Outcome monitoring may be considered for future implementation of guidelines.

Conflicts of interest

None.

Get With The Guidelines® - Resuscitation Investigators

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Mathias J. Holmberg and Lars W. Andersen were responsible for data acquisition, performed the statistical analyses, and drafted the manuscript. All authors contributed to the design of the study, interpreted the results, and critically revised the manuscript. All authors approved the final manuscript as submitted and agrees to be accountable for all aspects of the submitted work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.02.002.

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