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Clinical paper

The impact of time to amiodarone administration on survival from out-of-hospital cardiac arrest

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Abstract

Aim: To examine the impact of time to amiodarone administration on survival from shock-refractory Ventricular Fibrillation/pulseless Ventricular Tachycardia (VF/pVT) following out-of-hospital cardiac arrest (OHCA).

Methods: A retrospective cohort study of adult (≥16 years) OHCA patients in shock-refractory VF/pVT (after 3 consecutive defibrillation attempts) of medical aetiology who arrested between January 2010 and December 2019. Time-dependent propensity score matching was used to sequentially match patients who received amiodarone at any given minute of resuscitation with patients eligible to receive amiodarone during the same minute. Log-binomial regression models were used to assess the association between time of amiodarone administration (by quartiles of time-to-matching) and survival outcomes.

Results: A total of 2,026 patients were included, 1,393 (68.8%) of whom received amiodarone with a median (interquartile range) time to administration of 22.0 (18.0–27.0) minutes. Propensity score matching yielded 1,360 matched pairs. Amiodarone administration within 28 minutes of the emergency call was associated with a higher likelihood of return of spontaneous circulation (ROSC) (≤18minutes: RR = 1.03 (95%CI 1.02, 1.04); 19-22minutes: RR = 1.02 (95%CI 1.01, 1.03); 23-27minutes: RR = 1.01 (95%CI 1.00, 1.02)) and event survival (pulse on hospital arrival) (≤18 minutes: RR = 1.05 (95%CI 1.03, 1.07); 19–22 minutes: RR = 1.03 (95%CI 1.01, 1.05); 23–27 minutes: RR = 1.02 (95%CI 1.00, 1.03). Amiodarone administration within 23 minutes of the emergency call was associated with a higher likelihood of survival to hospital discharge (≤18minutes: RR = 1.17 (95%CI 1.09, 1.24; 19–22 minutes: RR = 1.10 (95%CI 1.04, 1.17).

Conclusion: Amiodarone administered within 23 minutes of the emergency call is associated with improved survival outcomes in shock-refractory VF/pVT, although prospective trials are required to confirm these findings.

Keywords: Amiodarone, Cardiac arrest, Cardiopulmonary resuscitation, Ventricular fibrillation, Refractory cardiac arrest

Introduction

Out of hospital cardiac arrests (OHCA) with an initial presentation of ventricular fibrillation (VF) and pulseless ventricular tachycardia (pVT) account for 20–27% of all cardiac arrests worldwide.[1–3] Although there is strong evidence to support the benefit of early CPR and defibrillation in the management of VF/pVT,[4,5] there is limited evidence to show that the administration of antiarrhythmic medication improves survival to hospital discharge outcomes. Administration of antiarrhythmic medication in cardiac arrest aims to increase the cardiac action potential duration and prolong the effective refractory period of cardiac cells to facilitate successful defibrillation and reduce the risk of recurrent arrhythmias.[6,7].

International guidelines currently suggest the use of amiodarone or lidocaine for VF/pVT that is unresponsive to defibrillation.[3,5,7,8] Amiodarone has been shown to improve the occurrence of return of spontaneous circulation (ROSC) and survival to hospital admission.[3,5,7–15] However, randomised controlled trials of antiarrhythmic medication are yet to demonstrate an improvement in survival to hospital discharge or favourable neurological outcome in shock-refractory VF/pVT.[3,5,7–18] Importantly, there is inconsistency in the literature about when amiodarone should be administered.[3,5,7,15] A growing body of evidence suggests that the earlier administration of amiodarone is associated with improved patient outcomes.[19–23]

The European Resuscitation Council recommends 300 mg intravenous or intraosseous amiodarone after three defibrillation attempts

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and a further 150 mg after five defibrillation attempts.[8] However, these recommendations are based on studies performed when three stacked defibrillation attempts were suggested.[24,25] In contrast, the 2018 American Heart Association update defined shock-refractory VF/pVT as VF or pVT that persists or recurs after one or more defibrillations.[7] The 2020 American Heart Association guidelines acknowledge a potential time dependent benefit of amiodarone administration, but the algorithm still recommends administration after three defibrillations.[5] Evidence is still emerging on how amiodarone administration timing affects patient outcomes such as ROSC, survival to hospital admission, event survival (pulse at hospital arrival), and favourable neurological outcome.

In this study, we sought to determine the impact of prehospital amiodarone administration timing on ROSC, event survival and survival to hospital discharge among patients with shock-refractory VF/pVT OHCA.

Methods

Study design

This was a retrospective cohort study of adult patients (≥16 years of age) with shock-refractory VF/pVT who were treated by emergency medical services (EMS) between January 2010 and December 2019 in Victoria, Australia. Patients were excluded if they did not receive an attempted resuscitation by EMS, received their first defibrillation from a first responder or public access defibrillator prior to paramedic arrival, achieved ROSC or changed to non-shockable rhythm prior to fourth defibrillation, or suffered an OHCA from a traumatic cause. This study was approved by the Monash University Human Research Ethics Committee (Project Number 22255).

Setting

Ambulance Victoria is a single state-wide provider of EMS in the state of Victoria, Australia. The EMS serves a population of over 6.6 million people across 227,600 km^2. In suspected OHCA events there is a dual dispatch of paramedics with Advanced Life Support (ALS) skills (who can perform basic life support and administer intravenous epinephrine, fluids, and utilise a supraglottic airway device) and Intensive Care Paramedic (ICP) skills (who can perform endotracheal intubation, cricothyroidotomy, establish intraosseous access, and administer a broader range of medications, including amiodarone). Community volunteer responders and firefighters may also respond to suspected cardiac arrests to provide basic life support prior to ambulance arrival. Paramedics operate under clinical practice guidelines which follow the recommendations of the Australian Resuscitation Council.[26] In the setting of VF/pVT OHCA, Ambulance Victoria currently recommends the administration of 300 mg amiodarone if VF/pVT persists after the 3rd defibrillation, and an additional 150 mg amiodarone if VF/pVT persists after the 5th defibrillation.

Data sources

This study used data from the Victorian Ambulance Cardiac Arrest Registry (VACAR), a population-based register of all OHCA events attended by EMS in Victoria. The methodology has been described in detail elsewhere.[27] OHCA cases attended by EMS are identified by a sensitive search strategy using data from electronic patient care records. Cases are entered into the registry by trained personnel according to Utstein consensus definitions.[28] VACAR also collects patient discharge outcomes from hospital records for patients transported to hospital.

Definitions

Shock-refractory VF/pVT was defined as a persistent shockable rhythm after three defibrillation attempts (i.e. received four or more consecutive defibrillations). We stratified the population into two groups: patients who received prehospital amiodarone during their shock-refractory VF/pVT episode (i.e. prior to ROSC or rhythm deterioration), and patients who did not. Patients who received prehospital amiodarone following a recurrent VF/pVT episode were therefore included in the 'no amiodarone' group.

Time-dependent propensity score matching

To assess the association between time to amiodarone administration and survival outcomes (survival to hospital discharge, event survival and ROSC), we used time-dependent propensity score matching.[29] This approach has been used previously in OHCA research to account for resuscitation time bias.[30] The propensity score was calculated as the cumulative incidence function of a Fine-Gray competing-risks regression model.[31] In this model, time from receipt of the emergency phone call to administration of amiodarone was the dependent variable. Termination of VF/pVT prior to the administration of amiodarone was included as a competing risk. This analysis was adjusted for relevant patient factors and year of cardiac arrest (all variables presented in Table 1). For patients witnessed to arrest by EMS, we used the time from commencement of CPR instead of receipt of the emergency phone call. Age (in years) was included as a restricted cubic spline with four knots (at 39, 60, 72 and 87 years) to accommodate its non-linear relationship with the likelihood of being treated with amiodarone. EMS response time was set to zero minutes for arrests witnessed by EMS. All variables were entered as non-time-dependent except for EMS response time, time to first defibrillation, time to first epinephrine administration, and time to ICP arrival, which were entered as time-dependent covariates.

Next, 1:1 risk-set matching was performed on the propensity score using nearest neighbour matching with a maximum calliper width within 0.01 of the propensity score. We tested calliper widths of 0.1 and 0.001 of the propensity score, however a width of 0.01 was determined to achieve the best balance between the treated and untreated groups. Patients receiving amiodarone at any given minute (from 2 to 69 minutes) were matched without replacement with a patient eligible to receive amiodarone in the same minute.[32] Patients eligible to receive amiodarone included those who received amiodarone later in their resuscitation attempt, as well as patients who did not receive any amiodarone. To assess the performance of the matching, we calculated standardised differences of the baseline characteristics presented in Table 1. A standardised difference of less than 0.1 is generally considered to represent good balance,[33] however we accepted a standardised difference of less than 0.25 as has been done previously.[34,35]

Statistical analysis

The primary outcome was survival to hospital discharge. The secondary outcomes included prehospital ROSC and event survival (a pulse on arrival at hospital). Categorical variables are presented as frequencies and proportions. Continuous variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate.

Table 1 – Baseline characteristics in the full and matched cohorts.

	Full cohort				Matched cohort		
	Total (*n* = 2,026)	Amiodarone (*n* = 1,393)	No amiodarone (*n* = 633)	Standardized difference	Amiodarone (*n* = 1,360)	At risk of receiving amiodarone (*n* = 1,360)	Standardized difference
Age, mean (SD)	65.0 (14.6)	64.5 (14.4)	66.1 (15.0)	0.108	64.5 (14.4)	64.3 (14.5)	0.012
Male sex, *n* (%)	1,662 (82.0)	1,168 (83.9)	494 (78.0)	0.148	1,143 (84.0)	1,158 (85.2)	0.031
Year of arrest, *n* (%)				0.038			0.078
2010	235 (11.6)	167 (12.0)	68 (10.7)		166 (12.2)	190 (14.0)	
2011	222 (11.0)	158 (11.3)	64 (10.1)		154 (11.3)	166 (12.2)	
2012	207 (10.2)	145 (10.4)	62 (9.8)		139 (10.2)	146 (10.7)	
2013	208 (10.3)	147 (10.6)	61 (9.6)		142 (10.4)	147 (10.8)	
2014	190 (9.4)	121 (8.7)	69 (10.9)		121 (8.9)	131 (9.6)	
2015	215 (10.6)	142 (10.2)	73 (11.5)		138 (10.2)	131 (9.6)	
2016	185 (9.1)	119 (8.5)	66 (10.4)		119 (8.8)	96 (7.1)	
2017	176 (8.7)	124 (8.9)	52 (8.2)		117 (8.6)	109 (8.0)	
2018	186 (9.2)	132 (9.5)	54 (8.5)		128 (9.4)	112 (8.2)	
2019	202 (10.0)	138 (9.9)	64 (10.1)		136 (10.0)	132 (9.7)	
Season, *n* (%)				0.004			0.005
Summer	460 (22.7)	314 (22.5)	146 (23.1)		302 (22.2)	305 (22.4)	
Autumn	560 (27.6)	396 (28.4)	164 (25.9)		393 (28.9)	386 (28.4)	
Winter	524 (25.9)	347 (24.9)	177 (28.0)		344 (25.3)	341 (25.1)	
Spring	482 (23.8)	336 (24.1)	146 (23.1)		321 (23.6)	328 (24.1)	
Presumed cardiac aetiology, *n* (%)	1,950 (96.3)	1,343 (96.4)	607 (95.9)	0.027	1,306 (96.0)	1,313 (96.5)	0.027
Witness, *n* (%)				0.043			0.005
Unwitnessed	450 (22.3)	315 (22.7)	135 (21.4)		313 (23.0)	301 (22.1)	
Bystander witnessed	1,453 (72.1)	997 (71.9)	456 (72.4)		986 (72.5)	1,007 (74.0)	
EMS witnessed	113 (5.6)	74 (5.3)	39 (6.2)		61 (4.5)	52 (3.8)	
Missing (*n*)	10	7	3		0	0	
Bystander CPR, *n* (%)*	1,494 (78.1)	1,045 (79.2)	449 (75.6)	0.087	1,026 (79.0)	1,070 (81.8)	0.071
Public location, *n* (%)	582 (28.7)	395 (28.4)	187 (29.5)	0.026	385 (28.3)	330 (24.3)	0.092
Metropolitan region, *n* (%)	1,419 (70.0)	1,062 (76.2)	357 (56.4)	0.429	1,045 (76.8)	956 (70.3)	0.149
EMS response time, median (IQR)^	7.9 (5.9–10.4)	7.9 (5.9–10.4)	7.7 (5.9–10.6)	0.068	7.9 (6.0–10.3)	8.3 (6.3–10.8)	0.108
Time from call to first defibrillation, median (IQR)^	11.0 (9.0–14.0)	11.0 (9.0–14.0)	11.0 (8.0–14.0)	0.020	11.0 (9.0–14.0)	12.0 (9.0–14.0)	0.138
Missing (*n*)	3	2	1		2	0	
ICP arrival, *n* (%)	1,927 (95.1)	1,384 (99.4)	543 (85.8)	0.535	1,351 (99.3)	1,354 (99.6)	0.030
Time from call to ICP arrival, median (IQR)^	13.0 (10.0–18.0)	12.0 (10.0–16.0)	15.0 (11.0–23.0)	0.454	12.0 (10.0–16.0)	13.0 (10.0–17.0)	0.081
Epinephrine administered, *n* (%)	1,903 (93.9)	1,390 (99.8)	513 (81.0)	0.671	1,357 (99.8)	1,356 (99.7)	0.015
Time from call to first epinephrine administration, median (IQR)^	18.0 (15.0–23.0)	18.0 (15.0–21.0)	20.0 (16.0–26.0)	0.448	18.0 (15.0–21.0)	18.0 (15.0–22.0)	0.107
Time from call to amiodarone administration, median (IQR)^	22.0 (18.0–27.0)	22.0 (18.0–27.0)	n/a	n/a	n/a	n/a	n/a

Abbreviations: SD, standard deviation; EMS, emergency medical service; CPR, cardiopulmonary resuscitation; IQR, interquartile range; ICP, intensive care paramedic; n/a, not applicable.

* Excludes EMS witnessed cases.

^ For EMS witnessed cases, this represents the time from commencement of CPR.

Using the matched cohort, we constructed log-binomial regression models with robust standard errors to assess the association between time of amiodarone administration and the primary and secondary outcomes. The models included an interaction term between

amiodarone and quartiles of 'minute of matching' (≤18 minutes; 19–22 minutes; 23–27 minutes; ≥28 minutes). Within each quartile, we then estimated the likelihood of the primary and secondary outcomes for treated, relative to untreated, patients using the estimated regression coefficients. Results are presented as Risk Ratios (RR) and 95% Confidence Intervals (CI).

We conducted two sensitivity analyses. In the first, we performed the same analysis as above, however excluded unwitnessed and EMS witnessed cases. This analysis, which included only patients who were witnessed to arrest by a bystander, aimed to examine a more homogeneous group of patients for whom the time between emergency call and ambulance arrival was likely to be representative of the patient's true arrest duration. In this analysis, the time between emergency call and matching ranged between 9 and 55 minutes. In the second sensitivity analysis, we examined an alternative exposure variable defined as the time between the third consecutive defibrillation and amiodarone administration. For this analysis, we replicated the above methodology, where time 0 represented the minute during which defibrillation number 3 was delivered, and the time between emergency call and first defibrillation were entered as a non-time-dependent variables. This model did not adjust for EMS response time as it exhibited collinearity with time to first defibrillation. Continuous variables (age and time to first defibrillation) were included as restricted cubic splines with four knots. Time-dependent variables included time to first epinephrine administration and time to ICP arrival. Time to matching was assessed as a categorical term representing equal quartiles between the third consecutive shock and amiodarone administration (≤2 minutes; 3–4 minutes; 5–8 minutes; ≥9 minutes). All analyses were undertaken using Stata statistical software (version 17).

Results

Patient characteristics

A total of 2,026 adult patients presenting with VF/pVT OHCA were included in this study (Fig. 1). In total, 1,393 (68.8%) received amiodarone during the shock-refractory VF/pVT episode. The median time to amiodarone administration was 22.0 (IQR 18.0–27.0) minutes from the time of emergency call and 624 patients (44.8%) received amiodarone ≥23 minutes from the emergency call.

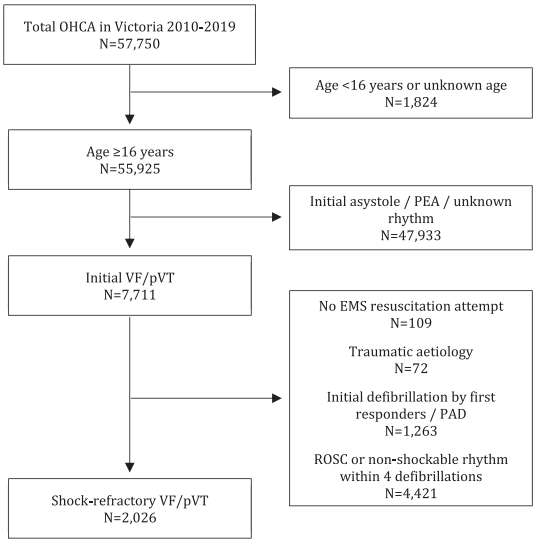

Fig. 1 – Patient selection flow chart.

Patient characteristics before and after matching are presented in Table 1. Before matching, patients receiving amiodarone were more likely to arrest in metropolitan Melbourne (76.2% vs. 56.4%), have ICP's on scene (99.4% vs. 85.8%), and receive epinephrine (99.8% vs. 81.0%). Propensity matching led to balanced arrest characteristics including: arrest in metropolitan Melbourne (76.8% vs. 70.3%); ICP attendance (99.3% vs. 99.6%); median time from call to ICP arrival (12 minutes (IQR 10–16) vs. 13 minutes (IQR 10–17)); epinephrine administration (99.8% vs. 99.7%); and median time to epinephrine administration (18 minutes (IQR 15–21) vs 18 minutes (IQR 15–22)).

Outcomes in matched cohort

Within the matched cohort, amiodarone administration within 28 minutes of the emergency call was associated with a higher likelihood of ROSC (≤18 minutes: RR = 1.031 (95% CI 1.018–1.043); 19–22 minutes: RR = 1.016 (95% CI 1.006–1.025); 23–27 minutes: RR = 1.010 (95% CI 1.002–1.018)) and event survival (≤18 minutes: RR = 1.046 (95% CI 1.025–1.067); 19–22 minutes: RR = 1.031 (95% CI 1.014–1.047); 23–27 minutes: RR = 1.015 (95% CI 1.001–1.029, Fig. 2). Furthermore, amiodarone administration within 23 minutes of the emergency call was associated with increased likelihood of survival to hospital discharge (≤18 minutes: RR = 1.166 (95% CI 1.092–1.244; 19–22 minutes: RR = 1.102 (95% CI 1.038–1.171). At or after 23 minutes from the emergency call, amiodarone administration was not associated with an improved likelihood of survival to hospital discharge.

Sensitivity analyses

The results of the sensitivity analysis involving bystander witnessed arrests are presented in Fig. 3 and corroborate the findings of the main analysis. Amiodarone administration within 28 minutes of the emergency call was associated with an increased likelihood of ROSC and event survival, whilst amiodarone administration within 23 minutes of the emergency call was associated with an increased likelihood of survival to hospital discharge.

The results of the second sensitivity analysis are presented in Fig. 4. Amiodarone administered ≤4 minutes after the 3rd defibrillation was associated with an increased likelihood of survival to hospital discharge (≤2 minutes after 3rd defibrillation: RR = 1.071 (95% CI 1.000–1.148); 3–4 minutes after 3rd defibrillation: RR = 1.094 (95% CI 1.031–1.161)).

Discussion

In this propensity matched analysis of shock-refractory VF/pVT OHCA, we observed a time-dependent relationship between amiodarone administration and survival outcomes, with earlier administration of amiodarone associated with higher survival outcomes. Amiodarone administration within 28 minutes of the emergency call was associated with an increased likelihood of ROSC and event survival, while administration of amiodarone within 23 minutes was associated with an increased likelihood of survival to hospital discharge. In our overall unmatched population, 44.8% of patients with shock-refractory VF/pVT received amiodarone ≥23 minutes from the emergency call. This indicates that almost half of patients received

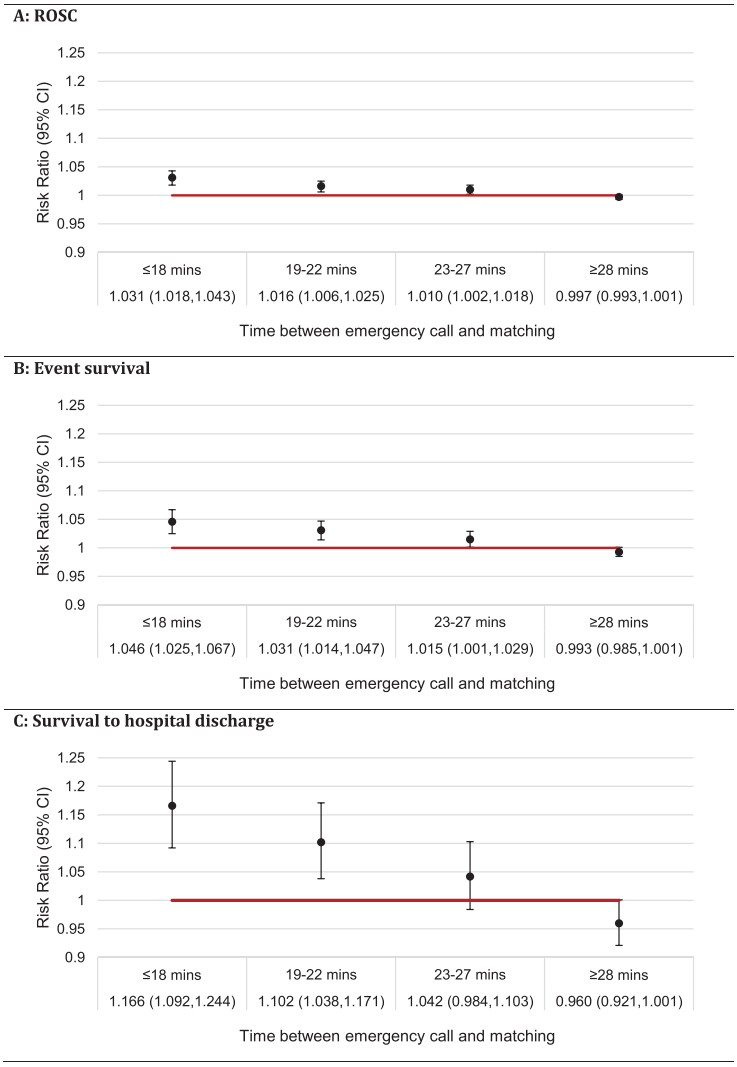

Fig. 2 – Association between minute of matching (from the emergency call) and survival outcomes.

amiodarone outside the timeframe which was associated with improved outcomes.

Several studies indicate that early administration of amiodarone in VF/pVT OHCA may be associated with improved patient outcomes.[10,14,15,19–23] For example, a sub-group analysis of patients who received early amiodarone demonstrated higher survival rates in the seminal ROC-ALPS trial (which compared amiodarone, lidocaine and placebo in VF/pVT OHCA). EMS witnessed OHCA patients were administered amiodarone in 11.7 ± 5.8 minutes, resulting in a higher incidence of survival to hospital discharge compared to placebo (risk difference 21.9%; 95% CI 5.8–38.0; $P = 0.01$).[15] This data indicates that even when accounting for early CPR and defibrillation in EMS witnessed OHCA, early amiodarone administration was associated with increased survival rates. In comparison, the overall average time from emergency call to amiodarone administration in the ROC-ALPS trial was 19.3 ± 7.1 minutes and did not demonstrate a significant difference in the rate of survival to hospital discharge compared to placebo.[15] A secondary analysis of the ROC ALPS trial showed that earlier administration of amiodarone is associated with higher rates of ROSC, event survival, survival to hospital discharge and improved neurological outcomes.[19,20]

It is postulated that antiarrhythmic medication alone is unlikely to pharmacologically convert VF/pVT to an organised perfusing rhythm, but rather, reduce the risk of recurrent arrhythmias after successful defibrillation.[7] Delays in antiarrhythmic administration could attenuate its effectiveness as the patient progresses into the metabolic phase of cardiac arrest, where cellular injury and physiological derangements may be irreversible despite restored circulation.[15,36] This highlights the need to minimise the timing of amiodarone administration. Prospective clinical trials are required to establish if amiodarone administration after one defibrillation or as soon as vascular access is obtained leads to better patient outcomes.

While the current clinical trials are yet to establish the ideal timing of amiodarone administration, our study findings indicate that earlier administration is associated with improved survival outcomes from refractory VF/pVT. This corroborates data from other studies which indicate improved ROSC,[22] event survival,[19,20,22,23] survival to discharge,[19,22,23] and good neurological outcome[19,22] when amiodarone is administered either less than 8 minutes of paramedic arrival with capacity to administer antiarrhythmic medication,[19] or from EMS call/dispatch within 19.5,[20] 20,[22] 23,[23] or 24 minutes.[14] Achieving early antiarrhythmic administration in practice is difficult

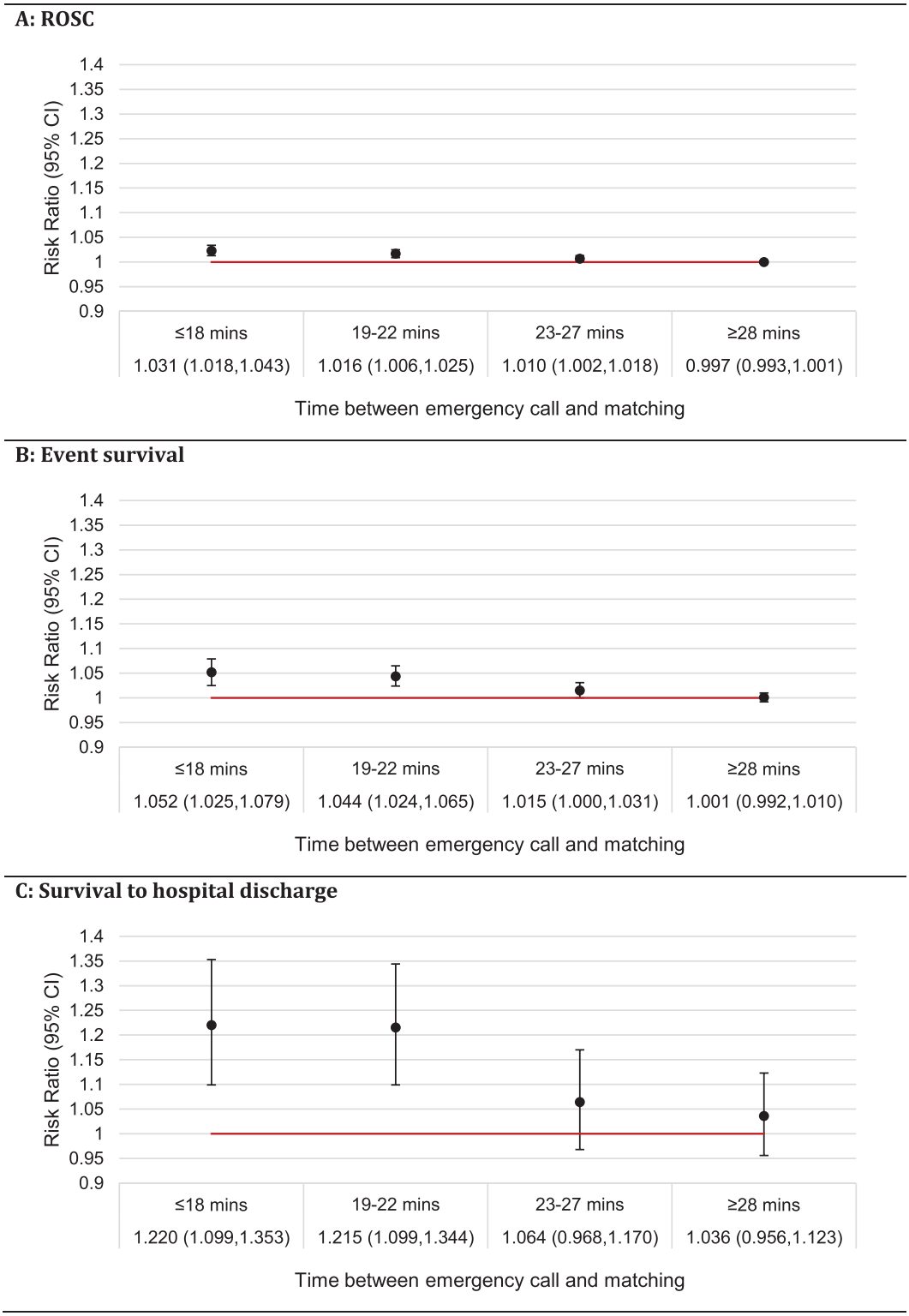

Fig. 3 – Association between minute of matching (from the emergency call) and survival outcomes in bystander witnessed OHCA.

for many EMS systems, with the obvious barrier being EMS response performance. Indeed, a reduction in response time may also significantly reduce the incidence of refractory VF/pVT.[37] For some EMS systems, including ours, there may be an opportunity to expand the use of amiodarone administration to all ALS paramedics, increasing the opportunity for its administration. Although ALS paramedics are currently able to administer intravenous epinephrine in our system, the use of amiodarone is limited to ICPs. However, the

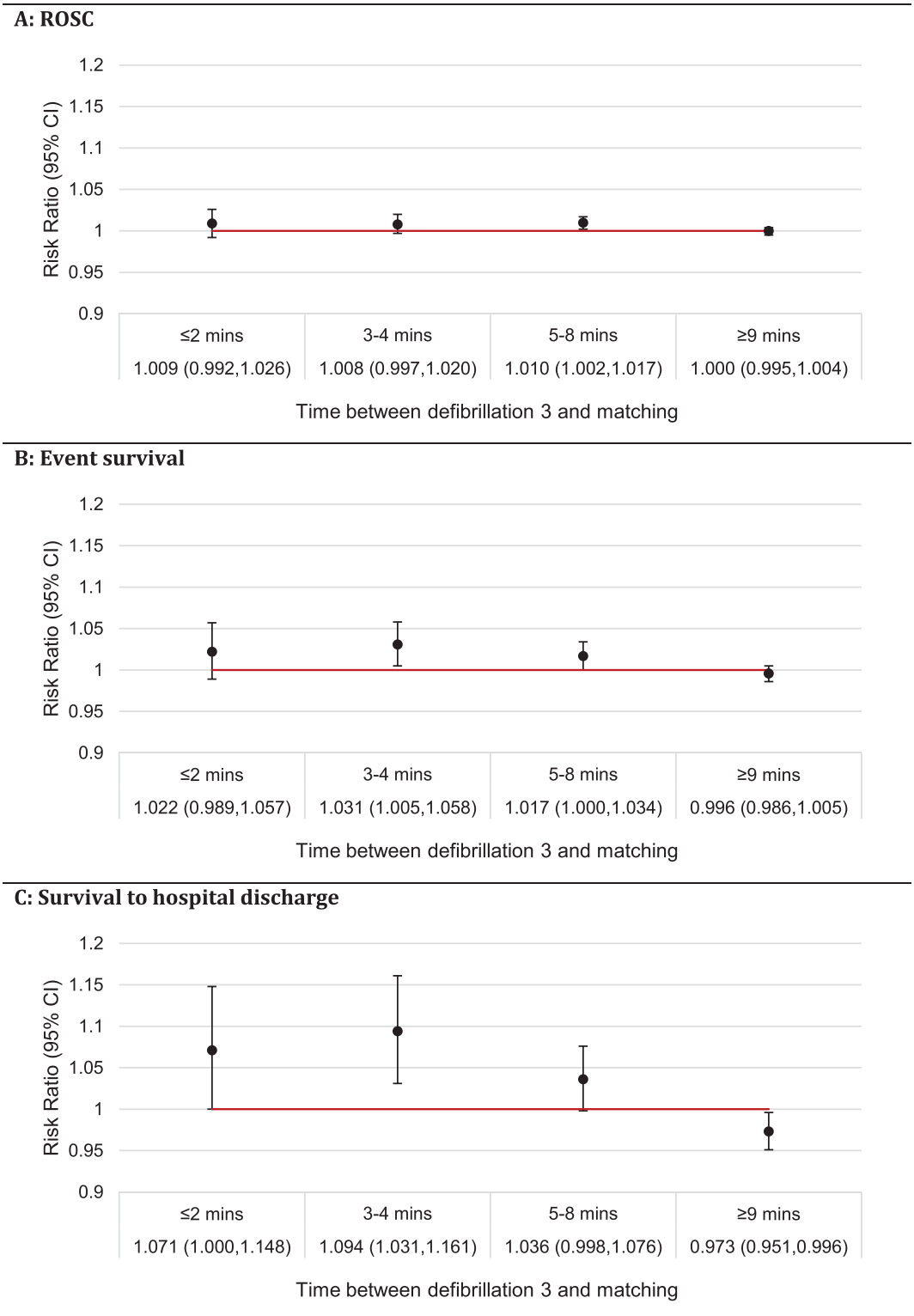

Fig. 4 – Association between minute of matching (from the third consecutive defibrillation) and survival outcomes.

introduction of additional priorities in low resource environments could also risk deteriorating CPR quality and defibrillation, and these risks should also be considered.

Limitations

This study has some limitations. It is retrospective and carries the associated limitations. The study is subject to bias in relation to the accuracy of documenting amiodarone and defibrillation timing on

the patient care record. Further, we excluded patients who received an initial defibrillation by first responders or public access defibrillation due to limited data around the timing of defibrillation and/or ROSC (n = 1,263). Our results may therefore under-estimate the effect of amiodarone on patient outcomes due to the exclusion of a higher-survival cohort. We have not examined the neurological outcome of patients who survived to hospital discharge. Data of hospital investigations and treatment were not collected and have the potential for unmeasured confounding. The study reflects local EMS treatment guidelines with amiodarone administration after three defibrillations. The effect of even earlier amiodarone administration after one defibrillation could therefore not be evaluated. The current presentation of amiodarone administered by the local EMS service uses the diluent polysorbate 80 which can cause hypotension.[3] The amiodarone diluent used in the ROC-ALPS trial was Captisol (a sulfobutyl ether ß-cyclodextrin) which is thought to reduce hypotensive effects.[3] The route of amiodarone administration was not recorded in this study. In a prespecified analysis of the data from the ROC-ALPS trial investigating the route of antiarrhythmic administration, survival to hospital discharge was increased when antiarrhythmics, relative to placebo, were administered via intravenous route compared to the intraosseous route.[38]

Conclusion

We observed administration of amiodarone within 28 minutes of the emergency call to be associated with improved ROSC and event survival outcomes, while administration within 23 minutes was associated with increased survival to hospital discharge. These results support information from the ROC-ALPS trial and recently published studies indicating a potential benefit of earlier amiodarone administration. An area which requires further investigation is the timing of amiodarone administration in relation to the number of defibrillations in VF/pVT. A randomised controlled trial could determine if early administration after at least 1 defibrillation improves patient outcome compared to current practice of administration after 3 defibrillations.

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CRediT authorship contribution statement

Elizabeth Perry: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Emily Nehme:** Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Dion Stub:** Writing – review & editing. **David Anderson:** Writing – review & editing. **Ziad Nehme:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'ZN is an editorial board member of Resuscitation Plus'.

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