Early Administration of Adrenaline for Out-of-Hospital Cardiac Arrest: A Systematic Review and Meta-Analysis

Liyu Ran, MD; Jinglun Liu, MD; Hideharu Tanaka, MD, PhD; Michael W. Hubble, PhD; Takyu Hiroshi, MD; Wei Huang, MD, PhD

BACKGROUND: The use of adrenaline in out-of-hospital cardiac arrest (OHCA) patients is still controversial. This study aimed to determine the effects of early pre-hospital adrenaline administration in OHCA patients.

METHODS AND RESULTS: PubMed, EMBASE, Google Scholar, and the Cochrane Library database were searched from study inception to February 2019 to identify studies that reported OHCA patients who received adrenaline. The primary outcome was survival to discharge, and the secondary outcomes were return of spontaneous circulation, favorable neurological outcome, and survival to hospital admission. A total of 574,392 patients were included from 24 studies. The use of early pre-hospital adrenaline administration in OHCA patients was associated with a significant increase in survival to discharge (risk ratio [RR], 1.62; 95% CI, 1.45–1.83; \( P < 0.001 \)) and return of spontaneous circulation (RR, 1.50; 95% CI, 1.36–1.67; \( P < 0.001 \)), as well as a favorable neurological outcome (RR, 2.09; 95% CI, 1.73–2.52; \( P < 0.001 \)). Patients with shockable rhythm cardiac arrest had a significantly higher rate of survival to discharge (RR, 5.86; 95% CI, 4.25–8.07; \( P < 0.001 \)) and more favorable neurological outcomes (RR, 5.10; 95% CI, 2.90–8.97; \( P < 0.001 \)) than non-shockable rhythm cardiac arrest patients.

CONCLUSIONS: Early pre-hospital administration of adrenaline to OHCA patients might increase the survival to discharge, return of spontaneous circulation, and favorable neurological outcomes.

REGISTRATION: URL: https://www.crd.york.ac.uk/PROSPERO; Unique identifier: CRD42019130542.

Key Words: adrenaline ■ early pre-hospital administration ■ out-of-hospital cardiac arrest

Out-of-hospital cardiac arrest (OHCA) remains a major public health problem in developed countries. Approximately 40,000 cases in Canada and 420,000 cases in the United States occur annually. Based on 81,864 cases in CARES (Cardiac Arrest Registry to Enhance Survival) 2018, the rate of survival to hospital discharge after OHCA treated by emergency medical services was 10.4%, with only 8.2% surviving with good functional status. The routine administration of adrenaline upon cardiac arrest has been recommended since 1974. The current American Heart Association and European Resuscitation Council guidelines for adult cardiac arrest state that 1 mg of adrenaline should be given every 3 to 5 minutes during resuscitation. The rationale for the use of adrenaline is that adrenaline was shown to increase aortic blood pressure and coronary perfusion pressure during chest compressions in animals and this result was also confirmed in humans. However, in recent years, the use of adrenaline has been brought into question because it may be associated with poor neurological outcomes, overall rates of return of spontaneous circulation (ROSCs) and survival to discharge.
Three systematic reviews have been conducted, and the results did not support adrenaline administration in OHCA patients. However, the association between outcomes and the time of adrenaline administration was unknown. The timing of adrenaline administration plays a key role in cardiac arrest resuscitation strategies. Observational studies have previously reported that the potential benefits of adrenaline may be limited for early-phase administration. It is believed that emphasis should be placed on the “time-dependent” effectiveness of adrenaline administration. Therefore, we conducted a systematic review and meta-analysis, aiming to determine the efficacy of early (time to adrenaline ≤10 minutes) pre-hospital adrenaline administration in OHCA patients.

### METHODS

The authors declare that all supporting data, analytic methods, and study materials within the article and the online supporting information are available to other researchers. This systematic review was performed in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA checklist is provided in Table S1. The study was registered with PROSPERO (International Prospective Register of Systematic Reviews; CRD42019130542). Institutional Review Board approval was not required for this systematic review and meta-analysis.

### Search Strategy and Study Eligibility

A systematic search of the scientific literature was performed. The search was conducted from inception to February 2019 in PubMed, EMBASE, Google Scholar, and the Cochrane Library database. The terms used for the search were as follows: ("heart arrest" OR "out-of-hospital cardiac arrest" OR "ventricular fibrillation" OR "pulseless electrical activity" OR "PEA" OR "asystole" OR "cardiac arrest") AND ("epinephrine" OR "adrenaline").

Studies were selected by 2 independent reviewers if they met the following inclusion criteria: (1) patients with OHCA were enrolled; (2) the patients were treated with epinephrine; (3) when multiple studies from the same institute were available, to avoid overlapping information, only the study with the largest sample size was included for each analysis; (4) randomized controlled trials (RCTs) or observational studies; and (5) the study outcomes were stated. Inter-reviewer agreement was determined using Cohen kappa coefficients.

### Outcomes

The primary outcome was survival to discharge. The secondary outcomes were ROSC, favorable neurological outcome at hospital discharge/1 month according to a cerebral performance category of 1 or 2, and survival to hospital admission.

### Risk of Bias Assessment

The Newcastle-Ottawa scale, which assesses the quality of non-randomized studies, was used to assess the risk of bias according to 3 aspects: selection, comparability, and outcome. Higher numbers of stars indicate better quality; the study quality was characterized as low (0–4 stars), moderate (5–6 stars), or high (7–9 stars). The Cochrane Handbook of Systematic Reviews
for intervention tool was used to assess the risk of bias in each RCT. This tool evaluates the biases of 7 items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We assessed the risk of bias for each domain as low, unclear, or high risk of bias.

**Statistical Analysis**

The efficacy was estimated for each study by the risk ratio (RR) along with its 95% CI. *P*<0.05 were considered significant. Heterogeneity was assessed based on the *I*² test (*I*²>50, implying substantial heterogeneity). Across the studies, if no significant heterogeneity (defined as *I*²<50%) was found, the results were combined with the fixed-effects model (Mantel–Haenszel); otherwise, the random-effects model (DerSimonian–Laird) was used. A sensitivity analysis was performed by serially excluding each study to determine its influence. STATA version 12.0 (StataCorp, College Station, TX) was used to evaluate the outcomes. Finally, the quality of evidence was assessed in accordance with the Grading of Recommendations Assessment, Development and Evaluation approach, to provide reliable evidence for clinical selection.

**Subgroup Analysis**

A subgroup analysis was performed, and the patients administered adrenaline were stratified by shockable
| Study                  | Country                  | Study Period     | Design     | Sample | Age, y | Initial Cardiac Rhythm n (%) | Cardiac cause (%) | Witnessed Arrest (%) | Bystander CPR (%) | Intervention                                                                 | Comparator                     |
|------------------------|--------------------------|------------------|------------|--------|--------|------------------------------|-------------------|----------------------|-------------------|-----------------------------------------------------------------------------|--------------------------------|
| Callaham et al, 1992   | United States            | 1990–1992        | RCT, MC    | 816    | 65±18.6| 24.4                         | 75.6              | NA                  | 52.3              | Adrenaline                                    | No adrenaline                   |
| Cantrell et al, 2013   | United States            | 2009             | Cohort, MC | 660    | 63.1±16.8| 24.2                           | 75.8              | NA                  | 53                | Administration of adrenaline <10 min | Administration of adrenaline >10 min |
| Dumas et al, 2014      | France                   | 2000–2012        | Cohort, SC | 1556   | 59.8±16 | 54.3                          | 45.7              | NA                  | 84.6              | Adrenaline                                    | No adrenaline                   |
| Ewy et al, 2015        | United States            | 2005–2013        | Cohort, MC | 3469   | 66.3±15.1| 41.8                           | 58.2              | 100                 | 100               | Administration of adrenaline in shockable rhythm | Administration of adrenaline in non-shockable rhythm |
| Fisk et al, 2018       | United States            | 2008–2016        | Cohort, SC | 2255   | 63.7±17.7| 24.6                           | 75.4              | NA                  | 36.6              | Administration of adrenaline in shockable rhythm | Administration of adrenaline in non-shockable rhythm |
| Funada et al, 2018     | Japan                    | 2011–2014        | Cohort, SC | 124 856| 77±14.8 | 0                              | 100               | 52.5                | 100               | Adrenaline                                    | No adrenaline                   |
| Gobet et al, 2015      | Japan                    | 2009–2010        | Cohort, MC | 209 577| 74±16.1 | 7.4                            | 92.6              | 56.7                | 35.7              | Adrenaline                                    | No adrenaline                   |
| Gueugniaud et al, 1998 | France and Belgium       | 1994–1996        | RCT, MC    | 3327   | 65.6±15 | 17                            | 68                | 71.6                | 78.8              | Standard doses of adrenaline | High doses of adrenaline |
| Gueugniaud, 2008       | France                   | 2004–2006        | RCT, MC    | 2894   | 61.5±15 | 9.2                            | 90.8              | 35.9                | 75.2              | Adrenaline                                    | Adrenaline+ vasopressin         |
| Guyette et al, 2004    | United States            | 2002–2003        | Cohort, SC | 298    | 63.8±15.1| 26.8                           | 68.8              | NA                  | 44                | Adrenaline                                    | No adrenaline                   |
| Hansen et al, 2015     | United States, Canada    | 2011–2015        | Cohort, MC | 32 101 | 68±19.5 | 0                              | 100               | 8.5                 | 40.2              | Administration of adrenaline <10 min | Administration of adrenaline >10 min |
| Hayashi et al, 2012    | Japan                    | 2007–2009        | Cohort, MC | 3161   | 73.3±15.2| 16                             | 84                | 67.3                | 100               | Adrenaline                                    | No adrenaline                   |
| Holmberg et al, 2002   | Sweden                   | 1990–1995        | Cohort, MC | 10 966 | 67.3    | 56.7                           | 43.3              | NA                  | 66.8              | Adrenaline                                    | No adrenaline                   |
| Hubble and Tyson, 2017 | United States            | 2012–2014        | Cohort, MC | 1917   | 66.3±14.8| 31                             | 69                | NA                  | 100               | Administration of adrenaline <10 min | Administration of adrenaline >10 min |
| Jacobs et al, 2011     | Australia                | 2006–2009        | RCT, SC    | 534    | 64.6±17.4| 49                             | 51                | 91.4                | 55.8              | Adrenaline                                    | Placebo                        |

(Continued)
| Study                      | Country          | Study Period   | Design    | Sample | Age, y | Initial Cardiac Rhythm n (%) | Cardiac cause (%) | Witnessed Arrest (%) | Bystander CPR (%) | Intervention                  | Comparator                      |
|----------------------------|------------------|----------------|-----------|--------|--------|-------------------------------|-------------------|-----------------------|-------------------|-------------------------------|--------------------------------|
| Bar-Joseph et al, 2005^16 | Israel           | 1990–1992      | RCT, MC   | 2122   | 65.7   | 49.4 (Shockable) 49 (Non-Shockable) | NA                | NA                    | 42                | Adrenaline and low sodium bicarbonate | Adrenaline and high sodium bicarbonate |
| Kosckí et al, 2013         | United States    | 2005–2011      | Cohort, MC| 686    | 69±17  | 25 (Shockable) 75 (Non-Shockable) | NA                | 47                    | NA                | Administration of Adrenaline <10 min | Administration of Adrenaline >10 min |
| Mukoyama et al, 2009^17    | Japan            | 2001–2006      | RCT, SC   | 336    | 65.4±17| 24 (Shockable) 76 (Non-Shockable) | 100               | 44.3                  | 15.1              | Adrenalin                        | Vasopressin                      |
| Nakahara et al, 2012^11    | Japan            | 2007–2008      | Cohort, MC| 49 165 | 76±15  | 16.4 (Shockable) 83.6 (Non-Shockable) | 67.5              | 100                   | 45.7              | Adrenaline                      | No adrenaline                    |
| Olavsteengen et al, 2012^11| Norway           | 2003–2008      | RCT, SC   | 848    | 66±18  | 33.5 (Shockable) 66.5 (Non-Shockable) | 71                | 65.3                  | 100               | Adrenaline                      | No adrenaline                    |
| Ong et al, 2007^18         | Singapore        | 2002–2004      | Cohort, MC| 1296   | 64±16  | 20.3 (Shockable) 79.7 (Non-Shockable) | NA                | 67.3                  | 19.4              | Adrenaline                      | No adrenaline                    |
| Ong et al, 2012^40         | Singapore        | 2006–2009      | RCT, MC   | 727    | 65±15  | 7.7 (Shockable) 88.2 (Non-Shockable) | 86.2              | 72.9                  | 15.4              | Adrenaline                      | Vasopressin                      |
| Tanaka et al, 2016^11      | Japan            | 2006–2012      | Cohort, MC| 119 639| 71±14  | 23.7 (Shockable) 76.3 (Non-Shockable) | 100               | 100                   | 45                | Adrenaline                      | No adrenaline                    |
| Wenzel et al, 2004^50      | Austria, Germany, Switzerland | 1999–2002 | RCT, MC   | 1186   | 66±14  | 39.8 (Shockable) 60.2 (Non-Shockable) | 60.6              | 77.6                  | 18.4              | Adrenaline                      | Vasopressin                      |

CPR indicates cardiopulmonary resuscitation; MC, multiple centers; NA, not applicable; Non-shockable, pulseless electrical activity and asystole; RCT, randomized controlled trial; SC, single center; and Shockable, ventricular fibrillation and pulseless ventricular tachycardia.
rhythm (ventricular fibrillation and pulseless ventricular tachycardia) and non-shockable rhythm (pulseless electrical activity and asystole).

**RESULTS**

**Study Selection**

Of the 3393 studies retrieved by the literature search, 349 duplicates were removed, leaving 3044 studies available for screening. After screening the title and abstract, 160 studies underwent full-text review. Of these studies, 9 randomized clinical trials and 15 observational studies were included. The search strategy is shown in Figure 1. The inter-reviewer agreement for the 5 inclusion criteria during the second review phase ranged from “good” to “very good” (κ: 0.768–1.000; Table S2).

**Study Characteristics**

The basic characteristics of the studies are summarized in Table. A total of 574 392 participants were included. Twenty-two studies included patients with shockable and non-shockable rhythms, and only 2 studies included patients with non-shockable rhythms. Eighteen studies only enrolled patients administered adrenaline; and 4 studies compared adrenaline to vasopressin. Eight studies reported outcomes where the time to adrenaline administration was within 10 minutes; 19 studies compared the outcomes between shockable and non-shockable rhythm patients. Four studies were based on data from the All-Japan Utstein Registry.

**Risk of Bias Assessment**

Fifteen adult cohorts were assessed for risk of bias using the Newcastle-Ottawa scale (Table S3). All studies were categorized as high quality. The potential sources of bias in RCTs are summarized in Figure S1 and displayed in Figure S2. Two RCTs were assessed as “low risk of bias”; 7 RCTs were assessed as having “unclear risk of bias” for at least 1 domain, and no study was assessed having a “high risk of bias.”

| Study ID | RR (95% CI) | Weight % |
|----------|-------------|----------|
| Hansen 2018 | 1.53 (1.30, 1.80) | 57.58 |
| Kosick 2019 | 1.43 (0.56, 3.64) | 1.55 |
| Nakahara 2012 | 1.91 (1.51, 2.42) | 19.10 |
| Hubble 2017 | 2.47 (1.81, 3.36) | 5.70 |
| Subtotal (I-squared = 65.0%, p = 0.036) | 1.68 (1.48, 1.90) | 83.93 |
| Kosick 2019 | 0.95 (0.20, 4.40) | 0.85 |
| Nakahara 2012 | 1.44 (1.04, 1.99) | 13.88 |
| Hubble 2017 | 0.72 (0.18, 2.90) | 1.34 |
| Subtotal (I-squared = 0.0%, p = 0.565) | 1.36 (1.00, 1.85) | 16.07 |
| Overall (I-squared = 49.1%, p = 0.067) | 1.62 (1.45, 1.83) | 100.00 |

Figure 2. Effects of early (<10 minutes vs >10 minutes) pre-hospital adrenaline administration on survival to discharge/1 month.

RR indicates risk ratio.
Adrenaline Administration Within 10 Minutes Versus Adrenaline Administration After 10 Minutes

The results of 4 studies\textsuperscript{19,23,36,37} were pooled to examine the effects of early adrenaline administration on survival to discharge, with a sample size of 28,700 in the shockable rhythm group and 5989 in the non-shockable rhythm group (Figure 2). A fixed-effects model was used; the pooled RR in the shockable rhythm group was 1.68 (95% CI, 1.48–1.90; \( P<0.001, I^2=65.0\% \)); in the non-shockable rhythm group, the pooled RR was 1.36 (95% CI, 1.00–1.85; \( P=0.053, I^2=0.0\% \)), indicating that a patient with shockable rhythm cardiac arrest receiving pre-hospital adrenaline within 10 minutes was 1.68 times more likely to survive to discharge than one receiving pre-hospital adrenaline after 10 minutes. The quality of the evidence was assessed as low (Figure S3).

Data from 4 studies\textsuperscript{19,21,34,36} were pooled for the analysis of pre-hospital ROSC, with a total of 6403 patients with shockable rhythm cardiac arrest and 17,179 patients with non-shockable rhythm cardiac arrest (Figure 3). A fixed-effects model was used, and the pooled RR in the shockable rhythm group was 1.58 (95% CI, 1.38–1.81; \( P<0.001, I^2=80.8\% \)); a sensitivity analysis was performed because of the significant heterogeneity when excluding the study\textsuperscript{21} that included only cardiac arrest patients. The heterogeneity decreased to 42.9\%, with a pooled RR of 1.35 (95% CI, 1.15–1.60; \( P<0.001 \)). In the non-shockable rhythm group, the pooled RR was 1.44 (95% CI, 1.23–1.68; \( P<0.001, I^2=0.0\% \)), indicating a greater likelihood of experiencing pre-hospital ROSC in patients administered pre-hospital adrenaline within 10 minutes. The quality of the evidence was assessed as low (Figure S3).

We included 5 studies\textsuperscript{18,21,35–37} in a pooled analysis of favorable neurological outcomes (cerebral performance category 1–2), with a total of 6302 patients with shockable rhythm cardiac arrest and 33,454 patients with non-shockable rhythm cardiac arrest (Figure 4). A fixed-effects model was used; the pooled RR in the shockable rhythm group was 3.21 (95% CI, 2.54–4.05, \( P=0.000; I^2=55.2\% \)), and the

| Study ID | RR (95% CI) | Weight |
|---------|------------|--------|
| Shockable |            |        |
| Kosick 2013\textsuperscript{19} | 1.38 (0.90, 2.11) | 7.68 |
| Tanaka 2016\textsuperscript{21} | 2.20 (1.74, 2.77) | 12.47 |
| Hubble 2017\textsuperscript{36} | 1.25 (1.03, 1.50) | 23.01 |
| Cantrell 2013\textsuperscript{34} | 2.15 (1.24, 3.72) | 2.90 |
| Subtotal (\textit{i}-squared = 80.8\%, \textit{p} = 0.001) | 1.58 (1.38, 1.81) | 46.07 |
| Non-shockable |            |        |
| Kosick 2013\textsuperscript{19} | 1.38 (0.97, 1.97) | 12.97 |
| Tanaka 2016\textsuperscript{21} | 1.64 (1.23, 2.19) | 15.03 |
| Hubble 2017\textsuperscript{36} | 1.27 (1.02, 1.58) | 21.75 |
| Cantrell 2013\textsuperscript{34} | 1.74 (1.00, 3.03) | 4.19 |
| Subtotal (\textit{i}-squared = 0.0\%, \textit{p} = 0.472) | 1.44 (1.23, 1.68) | 53.93 |
| Overall (\textit{i}-squared = 63.2\%, \textit{p} = 0.008) | 1.50 (1.36, 1.67) | 100.00 |

Figure 3. Forest plot for pooling the effects of early (<10 minutes vs >10 minutes) pre-hospital adrenaline administration on return of spontaneous circulation.
ROSC indicates return of spontaneous circulation; and RR, risk ratio.
pooled RR in the non-shockable rhythm group was 1.58 (95% CI, 1.20–2.09; P=0.001, I²=0.0%). This result suggested that a patient with shockable rhythm cardiac arrest receiving pre-hospital adrenaline within 10 minutes was 3.21 times more likely to experience a favorable neurological outcome than one receiving pre-hospital adrenaline after 10 minutes. The quality of the evidence was assessed as moderate (Figure S3). One study did not report initial cardiac rhythm separately; when the study was included, the pooled overall RR was 2.03 (95% CI, 1.73–2.39; P<0.001, I²=81.2%) (Figure S4).

### Shockable Rhythm Versus Non-Shockable Rhythm

Fourteen studies were included to observe the pooled effects of adrenaline administration on survival to discharge, with a sample size of 21 844 patients with shockable rhythm cardiac arrest and 208 284 patients with non-shockable rhythm cardiac arrest (Figure 5A). A random-effects model was used; the pooled RR was 5.86 (95% CI, 4.25–8.07; P<0.001, I²=89.6%), which indicated that a patient with shockable rhythm cardiac arrest was 5.86 times more likely to survive to discharge than one with non-shockable rhythm cardiac arrest. The quality of the evidence was assessed as high (Figure S5).

Fourteen studies were included to observe the pooled effects of adrenaline administration on pre-hospital ROSC, with a sample size of 19 480 patients with shockable rhythm cardiac arrest and 205 671 patients with non-shockable rhythm cardiac arrest (Figure 5B). A random-effects model was used; the pooled RR was 1.51 (95% CI, 0.91–2.50; P=0.11, I²=99.5%), and there was no significant difference between the groups. The quality of the evidence was assessed as high (Figure S5).

Eight studies were included to observe the pooled effects of adrenaline administration on favorable neurological outcome (cerebral performance category 1–2), with a sample size of 7317 patients with shockable rhythm cardiac arrest and 27 411 patients with non-shockable rhythm cardiac arrest (Figure 6A). A
Figure 5. A, Forest plot comparing survival to discharge between patients who had shockable and non-shockable rhythm cardiac arrest; B, Forest plot comparing return of spontaneous circulation between patients who had shockable and non-shockable rhythm cardiac arrest. ROSC indicates return of spontaneous circulation; and RR, risk ratio.
Figure 6. A, Forest plot comparing the effects of a cerebral performance category of 1 to 2 between patients who had shockable and non-shockable rhythm cardiac arrest; B, Forest plot comparing survival to admission between patients who had shockable and non-shockable rhythm cardiac arrest. RR indicates risk ratio.
random-effects model was used; the pooled RR was 5.10 (95% CI, 2.90–8.97; P<0.001, I²=94.1%), indicating that a patient with shockable rhythm cardiac arrest was 5.10 times more likely to experience a favorable neurological outcome than one with non-shockable rhythm cardiac arrest. The quality of the evidence was assessed as high (Figure S5).

Ten studies were included to observe the pooled effects of adrenaline administration on survival to admission, with a sample size of 2359 patients with shockable rhythm cardiac arrest and 9655 patients with non-shockable rhythm cardiac arrest (Figure 6B). A random-effects model was used; the pooled RR was 1.45 (95% CI, 1.33–1.58; P<0.001, I²=17.6%), suggesting a higher rate of survival to admission in patients with shockable rhythm cardiac arrest than in patients with non-shockable rhythm cardiac arrest. The quality of the evidence was assessed as high (Figure S5).

DISCUSSION

In this systematic review and meta-analysis, we evaluated the effects of early pre-hospital administration of adrenaline in OHCA patients. Our results indicated that the administration of adrenaline within 10 minutes significantly increased the survival to discharge, ROSC, and favorable neurological outcomes. In addition, compared with non-shockable cardiac arrest patients, shockable cardiac arrest patients seemed to have a significantly improved prognosis, especially in terms of survival to discharge and favorable neurological outcome.

The use of adrenaline has been reported to result in severe neurological impairment. In a recent randomized, double-blind trial,19 Perkins et al found that severe neurologic impairment was more frequent in the adrenaline group than in the placebo group (31.0% versus 17.8%). Although a more favorable neurologic outcome at discharge was observed in the adrenaline group than in the placebo group, the difference was not significant (2.2% versus 1.9%). In addition, these authors also reported a significantly higher rate of 30-day survival in the adrenaline group than in the placebo group. In another double-blind randomized controlled trial, Jacobs et al45 reported that although pre-hospital ROSC was significantly improved, the outcomes, including survival to discharge and favorable neurological survival, did not differ.

In contrast, in recent years, several studies have reported that a potential benefit of adrenaline was only seen with early administration.18–20,22,51,52 In a multicenter observational study,19 Hayashi et al reported that among shockable rhythm cardiac arrest patients, 66.7% of the patients who received adrenaline within 10 minutes had neurologically intact 1-month survival; however, the rate decreased to 24.9% in patients without adrenaline administration. Fukuda et al22 performed a similar propensity score-matched study of 237,068 patients; compared with the patients who did not receive adrenaline administration, the patients who received adrenaline within 15 minutes had a significantly higher rate of survival to 1 month and favorable neurological survival, regardless of whether the patients had shockable or non-shockable rhythm cardiac arrest. Our results are consistent with the results of these previous studies. In the present study, our findings supported the effects of early adrenaline administration on increasing survival to discharge, overall ROSC, and favorable neurological outcome.

The American Heart Association guidelines53 recommend that for cardiac arrest with a shockable rhythm, it may be reasonable to administer epinephrine after initial defibrillation attempts have failed. In our subgroup analysis stratified by initial cardiac arrest rhythm, early administration of adrenaline improved the outcomes in both shockable and non-shockable rhythm cardiac arrest patients. The patients with shockable rhythm cardiac arrest were found to have significantly higher rates of survival to discharge, favorable neurological outcomes and survival to admission than patients with non-shockable rhythm cardiac arrest in the adrenaline administration group. The different outcomes between the shockable and non-shockable rhythm groups might be because of the fact that defibrillation plays an important role in the prognosis of patients with shockable rhythm cardiac arrest; this difference indicates that when evaluating the effects of adrenaline, the initial cardiac rhythm should be considered a key factor for predicting the outcomes, and the patients should be stratified by initial cardiac arrest rhythm. Otherwise, this difference may influence the outcomes.

There were several potential limitations in this meta-analysis. First, our primary and secondary outcomes were based on a maximum of 3 to 4 studies, and only a few of the studies reported the effects of early adrenaline administration. Consequently, more studies are needed to confirm this conclusion. Second, most of the studies that were included were observational studies, making it difficult to adjust for confounders such as the number of doses provided, witnessed arrest, bystander cardiopulmonary resuscitation, emergency medical service response time, and the use of cointerventions. Third, interventions performed in the hospital, such as targeted temperature management and percutaneous coronary intervention, could not be measured or accounted for. Finally, because of insufficient data, we could not perform a comparison with a no adrenaline group; further studies are needed for this comparison.
Despite these limitations, the present study included a large sample size from 13 countries, which may help to increase the reliability of the results.

CONCLUSIONS

This systematic review and meta-analysis suggested that early pre-hospital administration of adrenaline in OHCA patients might increase the rate of survival to discharge, ROSC, and favorable neurologic outcomes. However, large randomized, controlled studies are needed to further confirm the results.

ARTICLE INFORMATION

Received August 19, 2019; accepted April 8, 2020.

Affiliations

From the Department of Orthopaedic Surgery and Orthopaedics Research Institute, West China Hospital, Sichuan University, Chengdu, China (L.R.); Department of Cardiology, First Affiliated Hospital, Chongqing Medical University, Chongqing, China (L.R., W.H.); Department of Emergency Medicine and Critical Care Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China (J.L.); Department of EMS System, Graduate School, Kokushikan University, Tokyo, Japan (H.T., T.H.); Emergency Medical Science Department, Wake Technical Community College, Raleigh, NC (M.W.H.).

Sources of Funding

This work is supported by the National Natural Science Foundation of China (81170188 and 30971212).

Disclosures

None.

Supplementary Materials

Tables S1–S3
Figures S1–S5
References 12, 18, 19, 21, 33, 35–40, 44, 45, 49, and 54

REFERENCES

1. Kitamura T, Iwami T, Kawamura T, Nagao K, Tanaka H, Hiraide A. Nationwide public-access defibrillation in Japan. N Engl J Med. 2010;362:994–1004.
2. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2005;112:1v1–203.
3. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiue SE, Cushman M, Delling FN, Deo R, et al.; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. Circulation. 2018;137:e67–e492.
4. Heart and Stroke Foundation of Canada. Statistics. 2015. Available at: http://www.HeartandStroke.com/. Last accessed July, 2015.
5. Centers for Disease Control and Prevention. 2018 cardiac arrest registry to enhance survival (CARES) national summary report. Available at: https://mycares.net/stepages/uploads/2019/2018%20NonTraum at%20National%20Summary%20Report.pdf. Accessed April 16, 2019.
6. Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). 3. Advanced life support. JAMA. 1994;272(supp):852–860.
7. Travers AH, Rea TD, Bobrow BJ, Edelson DP, Berg RA, Sayre MR, Berg MD, Chameides L, O’Connor RE, Swoor RA. Part 4: CPR overview: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation. 2010;122(S676–S684).
8. Redding JS, Pearson JW. Resuscitation from asphyxia. JAMA. 1962;182:283–286.
9. Redding JS, Pearson JW. Resuscitation from ventricular fibrillation. Drug therapy. JAMA. 1968;203:255–260.
10. Paradis NA, Martin GB, Rosenberg J, Rivers EP, Goetting MG, Appleton TJ, Feingold M, Cryer PE, Wortsman J, Nowak RM. The effect of standard- and high-dose epinephrine on coronary perfusion pressure during prolonged cardiopulmonary resuscitation. JAMA. 1991;265:1139–1144.
11. Olasveengen TM, Wilk L, Sunde K, Steen PA. Outcome when adrenaline (epinephrine) was actually given vs. not given—post hoc analysis of a randomized clinical trial. Resuscitation. 2012;83:327–332.
12. Dumas F, Bougouin W, Ceri G, Lamhaut L, Bougie A, Daviaud F, Moreau BT, Rosenberg J, Marjon E, Carli P, et al. Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? J Am Coll Cardiol. 2014;64:2360–2367.
13. Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. JAMA. 2012;307:1161–1168.
14. Perkins GD, Ji C, Deskin CD, Quinn T, Nolan JP, Scomparin C, Regan S, Long J, Slowther A, Pocock H, et al. A randomized trial of epinephrine in out-of-hospital cardiac arrest. N Engl J Med. 2018;379:711–721.
15. Lin S, Callaway CW, Shah PS, Wagner JD, Beyene J, Ziegler CP, Morrison LJ. Adrenaline for out-of-hospital cardiac arrest resuscitation: a systematic review and meta-analysis of randomized controlled trials. Resuscitation. 2014;85:732–740.
16. Akkasawapradt P, Rattanarsi S, McEvoy M, Graham CA, Sittichanbuncha Y, Thakkinstian A. Effects of prehospital adrenaline administration on out-of-hospital cardiac arrest outcomes: a systematic review and meta-analysis. Crit Care. 2014;18:463.
17. Loomba RS, Nijhawan K, Aggarwal S, Arora RR. Increased return of spontaneous circulation at the expense of neurologic outcomes: is pre-hospital epinephrine for out-of-hospital cardiac arrest really worth it? J Crit Care. 2015;30:1376–1381.
18. Hayashi Y, Iwami T, Kitamura T, Nishiuchi T, Kajino K, Sakai T, Nishiyama C, Nitta M, Hiraide A, Kaito T. Impact of early intravenous epinephrine administration on outcomes following out-of-hospital cardiac arrest. Circ J. 2012;76:1639–1645.
19. Kosicki C, Pinawin A, McGovern H, Allen D, Media DE, Ferguson T, Hopkins W, Sawyer KN, Boura J, Swor R. Rapid epinephrine administration improves early outcomes in out-of-hospital cardiac arrest. Resuscitation. 2013;84:915–920.
20. Donnino MW, Salciccioli JD, Howell MD, Cocchi MN, Giberson B, Berg K, Gautam S, Callaway C. Time to administration of epinephrine and outcome after in-hospital cardiac arrest with non-shockable rhythms: retrospective analysis of large in-hospital data registry. BMJ. 2014;348:g3026.
21. Tanaka H, Takyu H, Sagisaka R, Ueta H, Shirakawa T, Kinoshi T, Takahashi H, Nakagawa T, Shimazeki S, Ong Eng Hock M. Favorable neurological outcomes by early epinephrine administration within 19 minutes after EMS call for out-of-hospital cardiac arrest patients. Am J Emerg Med. 2016;34:2284–2290.
22. Fukuda T, Chashi FN, Matsubara T, Gunshin M, Kondo Y, Yahagi N. Effect of prehospital epinephrine on out-of-hospital cardiac arrest: a report from the national out-of-hospital cardiac arrest data registry in Japan, 2011–2012. Eur J Clin Pharmacol. 2016;72:1255–1264.
23. Hansen M, Schmicker RH, Newgard CD, Grunau B, Scheuermeier F, Cheskes S, Vithalani V, Alnaji F, Rea T, Idries AH. Time to epinephrine administration and survival from nonshockable out-of-hospital cardiac arrest among children and adults. Circulation. 2018;137:2032–2040.
24. Carron PN, Heymann E, Hugh O. Adrenaline in out-of-hospital cardiac arrest. Resuscitation. 2014;85:1717.
25. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:123–130.
26. Phelps R, Dumas F, Maynard C, Silver J, Rea T. Cerebral performance category and long-term prognosis following out-of-hospital cardiac arrest. Crit Care Med. 2013;41:1252–1257.
27. Jacobs I, Nadkarni V, Bahr J, Berg RA, Bill JE, Bossaert L, Cassan P, Coovadia A, D’Este K, Finn J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries: a statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian
28. Wells GA, Shea BJ, O’Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. *Appl Ergon.* 2000;31:727–734.

29. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org.

30. Overton RC. A comparison of fixed-effects and mixed (random-effects) models for meta-analysis tests of moderator variable effects. *Psychol Methods.* 1998;3:354–379.

31. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials.* 2007;28:105–114.

32. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, et al. Grade guidelines: 1. Introduction-grade evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64:383–394.

33. Ewy GA, Bobrow BJ, Chikani V, Sanders AB, Otto CW, Spalte DW, Kern KB. The time dependent association of adrenaline administration and survival from out-of-hospital cardiac arrest. *Resuscitation.* 2015;96:180–185.

34. Cantrell CL Jr, Hubble MW, Richards ME. Impact of delayed and infrequent administration of vasopressor on return of spontaneous circulation during out-of-hospital cardiac arrest. *Prehosp Emerg Care.* 2013;17:15–22.

35. Funada A, Goto Y, Tada H, Shimojima M, Hayashi K, Kawashiri MA, Yamagishi M. Effects of prehospital epinephrine administration on neurologically intact survival in bystander-witnessed out-of-hospital cardiac arrest patients with non-shockable rhythm depend on prehospital cardiopulmonary resuscitation duration required to hospital arrival. *Heart Vessels.* 2018;33:1525–1533.

36. Hubble MW, Tyson C. Impact of early vaspressor administration on neurological outcomes after prolonged out-of-hospital cardiac arrest. *Prehosp Disaster Med.* 2017;32:297–304.

37. Nakahara S, Tomio J, Nishida M, Morimura N, Ichikawa M, Sakamoto T. Association between timing of epinephrine administration and intact neurologic survival following out-of-hospital cardiac arrest in Japan: a population-based prospective observational study. *Acad Emerg Med.* 2012;19:782–792.

38. Callaham M, Madsen CD, Barton CW, Saunders CE, Pointer J. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. *JAMA.* 1992;268:2667–2672.

39. Fisk CA, Otsuka M, Yin L, McCoy AM, Latimer AJ, Maynard C, Nichol G, Larsen J, Cobb LA, Sayre MR. Lower-dose epinephrine administration and out-of-hospital cardiac arrest outcomes. *Resuscitation.* 2018;124:43–48.

40. Goto Y, Maeda T, Goto VN. Effects of prehospital epinephrine during out-of-hospital cardiac arrest with initial nonshockable rhythm: an observational cohort study. *Crit Care.* 2013;17:R188.

41. Gueugniaud PY, Mols P, Goldstein P, Pham E, Dubien PY, Deweerdt C, Vergnion M, Petit P, Carli P. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. *European Epinephrine Study Group.* *N Engl J Med.* 1998;339:1595–1601.

42. Gueugniaud PY, David JS, Chanzy E, Hubert H, Dubien PY, Mauriacourt P, Bragagna C, Billères X, Cloitou-Lambert MP, Fuster P, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med.* 2004;350:21–30.

43. Guyette FX, Guimond GE, Hostier D, Callaway CW. Vasopressin administered with epinephrine is associated with a return of a pulse in out-of-hospital cardiac arrest. *Resuscitation.* 2004;63:277–282.

44. Holmberg M, Holmberg S, Herlitz J. Low chance of survival among patients requiring adrenaline (epinephrine) or intubation after out-of-hospital cardiac arrest in Sweden. *Resuscitation.* 2002;54:37–45.

45. Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: a randomised double-blind placebo-controlled trial. *Resuscitation.* 2011;82:1138–1143.

46. Bar-Joseph G, Abramson NS, Kelsey SF, Mashiac h T, Craig MT, Safar P. Improved resuscitation outcome in emergency medical systems with increased usage of sodium bicarbonate during cardiopulmonary resuscitation. *Acta Anaesthesiol Scand.* 2005;49:6–15.

47. Mukoyama T, Kinoshita K, Nagao K, Tanjoh K. Reduced effectiveness of vasopressin in repeated doses for patients undergoing prolonged cardiopulmonary resuscitation. *Resuscitation.* 2009;80:755–761.

48. Ong ME, Tan EH, Ng FS, Panchal A, Lim SH, Manning PG, Ong VY, Lim SH, Yap S, Tham LP, et al. Survival outcomes with the introduction of intravenous epinephrine in the management of out-of-hospital cardiac arrest. *Ann Emerg Med.* 2007;50:635–642.

49. Ong ME, Tiah L, Leong BS, Tan EC, Ong VY, Tan EA, Poh BY, Pek PP, Chen Y. A randomised, double-blind, multi-centre trial comparing vasopressin and adrenaline in patients with cardiac arrest presenting to or in the emergency department. *Resuscitation.* 2012;83:953–960.

50. Wenzel V, Krismer AC, Amzr HR, Sitter H, Stadbauer KH, Lindner KH. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *Resuscitation.* 2004;55:105–113.

51. Andersson LW, Berg KM, Saindon BZ, Massaro JM, Raymond TT, Berg RA, Nådén VM, Donnino MW. Time to epinephrine and survival after pediatric in-hospital cardiac arrest. *JAMA.* 2015;314:802–810.

52. Hansen ML, Schmicker R, Newgard C, Rea TD, Egan D, Herren H, Grunau B, Scheuemeyer F, Cheskes S, Hutchinson J, et al. Time to epinephrine administration and survival from out-of-hospital cardiac arrests presenting with non-shockable rhythms. *Circulation.* 2017;136:A15533.

53. Panchal AR, Berg KM, Hirsch KG, Kudenchuk PJ, Del Rios M, Cabanas JG, Link MS, Kurz MC, Chan PS, Morley PT, et al. 2019 American Heart Association focused update on advanced cardiorespiratory life support: use of advanced airways, vasopressors, and extracorporeal cardiopulmonary resuscitation during cardiac arrest: an update to the American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2019;140:e881–e894.
Table S1. PRISMA checklist.

| Checklist item                                                                 | Reported on page |  |
|---------------------------------------------------------------------------------|-----------------|---|
| **TITLE**                                                                       |                 |   |
| Title                                                                            | 1               | 1 |
| **ABSTRACT**                                                                    |                 |   |
| Structured summary                                                              | 2               | 2 |
| Provide a structured summary including, as applicable: background; objectives;  |                 |   |
| data sources; study eligibility criteria, participants, and interventions; study |                 |   |
| appraisal and synthesis methods; results; limitations; conclusions and implications |                 |   |
| of key findings; systematic review registration number.                          |                 |   |
| **INTRODUCTION**                                                                |                 |   |
| Rationale                                                                        | 3               | 5 |
| Describe the rationale for the review in the context of what is already known.   |                 |   |
| Objectives                                                                       | 4               | 6 |
| Provide an explicit statement of questions being addressed with reference to     |                 |   |
| participants, interventions, comparisons, outcomes, and study design (PICOS).     |                 |   |
| **METHODS**                                                                     |                 |   |
| Protocol and registration                                                        | 5               | 6 |
| Indicate if a review protocol exists, if and where it can be accessed (e.g., Web |                 |   |
| address), and, if available, provide registration information including           |                 |   |
| registration number.                                                             |                 |   |
| Eligibility criteria                                                             | 6               | 6-7 |
| Specify study characteristics (e.g., PICOS, length of follow-up) and report      |                 |   |
| characteristics (e.g., years considered, language, publication status) used as   |                 |   |
| criteria for eligibility, giving rationale.                                      |                 |   |
| Information sources                                                              | 7               | 6 |
| Describe all information sources (e.g., databases with dates of coverage, contact |                 |   |
| with study authors to identify additional studies) in the search and date last    |                 |   |
| searched.                                                                        |                 |   |
| Section/topic                  | Checklist item | Reported on page # |
|--------------------------------|----------------|--------------------|
| Search                        | 8              | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 6 |
| Study selection               | 9              | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 6 |
| Data collection process       | 10             | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7 |
| Data items                    | 11             | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7 |
| Risk of bias in individual studies | 12          | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 7-8 |
| Summary measures              | 13             | State the principal summary measures (e.g., risk ratio, difference in means). | 8 |
| Synthesis of results          | 14             | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2), for each meta-analysis. | 8 |
| Risk of bias across studies   | 15             | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 8 |
| Additional analyses           | 16             | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 8 |

RESULTS
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. |
|-----------------|----|----------------------------------------------------------------------------------------------------------------------------------|
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). |

**DISCUSSION**

| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). |
|---------------------|----|----------------------------------------------------------------------------------------------------------------------------------|
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. |

**FUNDING**
Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.
| Criterion                        | Kappa | Standard error | P-value |
|---------------------------------|-------|----------------|---------|
| Patients with OHCA              | 1.000 | -              | -       |
| Treated with epinephrine        | 0.949 | 0.036          | 0.000   |
| Study population                | 1.000 | -              | -       |
| RCT or observational study      | 1.000 | -              | -       |
| Study outcome stated            | 0.768 | 0.070          | 0.000   |
Table S3. Newcastle-Ottawa Scale quality assessment scores for the included studies.

| First Author       | Selection (0-4) | Comparability (0-2) | Outcome (0-3) | Total stars |
|--------------------|-----------------|---------------------|---------------|-------------|
| Cantrell, 2013     | ★★★            | ★★                  | ★★★           | 8           |
| Dumas, 2014        | ★★★            | ★★                  | ★★★           | 8           |
| Ewy, 2015          | ★★★            | ★★                  | ★★★           | 8           |
| Fisk, 2018         | ★★★            | ★★                  | ★★★           | 8           |
| Funada, 2018       | ★★★★           | ★★                  | ★★★           | 9           |
| Goto, 2013         | ★★★★           | ★★                  | ★★★           | 9           |
| Guyette, 2004      | ★★★            | ★★                  | ★★★           | 8           |
| Hansen, 2018       | ★★★            | ★★                  | ★★★           | 8           |
| Hayashi, 2012      | ★★★★           | ★★                  | ★★★           | 9           |
| Holmberg, 2002     | ★★★            | ★★                  | ★★★           | 8           |
| Hubble, 2017       | ★★★            | ★★                  | ★★★           | 8           |
| Koscik, 2013       | ★★★            | ★★                  | ★★★           | 8           |
| Nakahara, 2012     | ★★★            | ★★                  | ★★★           | 8           |
| Ong, 2007          | ★★★★           | ★★                  | ★★★           | 9           |
| Tanaka, 2016       | ★★★★           | ★★                  | ★★★           | 9           |
Figure S1. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

| Study              | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|--------------------|---------------------------------------------|------------------------------------------|----------------------------------------------------------|-----------------------------------------------|----------------------------------------|-------------------------------------|------------|
| Callaham 1992      | +                                           | +                                       | +                                                        | +                                             | +                                      | +                                  | ?          |
| Guenugniaud 1998   | ?                                           | +                                       | +                                                        | +                                             | +                                      | +                                  | ?          |
| Gueugniaud 2008    | +                                           | +                                       | ?                                                        | +                                             | +                                      | +                                  | ?          |
| Jacobs 2011        | +                                           | +                                       | +                                                        | +                                             | +                                      | +                                  | +          |
| Joseph 2005        | ?                                           | ?                                       | ?                                                        | ?                                             | +                                      | +                                  | ?          |
| Mukoyama 2009      | ?                                           | ?                                       | ?                                                        | ?                                             | +                                      | +                                  | ?          |
| Olasveengen 2012   | ?                                           | ?                                       | ?                                                        | ?                                             | +                                      | +                                  | ?          |
| Ong 2012           | +                                           | +                                       | +                                                        | +                                             | +                                      | +                                  |            |
| Wenzel 2004        | +                                           | +                                       | +                                                        | +                                             | +                                      | +                                  | ?          |
Figure S2. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
## Figure S3. GRADE Assessment.

| Certainty assessment | N of patients | Effect | Certainty | Importance |
|----------------------|---------------|--------|-----------|------------|
|                       |               |        | Risk of bias |             |            |
|                       |               |        | Inconsistency |             |            |
|                       |               |        | Indirectness |             |            |
|                       |               |        | Imprecision |             |            |
|                       |               |        | Other considerations | Relative Risk (RR) | Absolute Risk (AR) |
|                       |               |        |             | (95% CI) | (95% CI) |
|                       |               |        |             | (95% CI) | (95% CI) |
|                       |               |        |             | (95% CI) | (95% CI) |
|                       |               |        |             | (95% CI) | (95% CI) |

**BG0C**

| 4 | observational studies | not serious | not serious | not serious | none | 27/36/35 (60.7%) | 46/83/0/0/9 (22.1%) | RR 1.61 (1.23-2.1) | 125 more per 1,000 (95% CI 113 233 events) | **B**\(\infty\) | LOW |

**CPC 1:2**

| 5 | observational studies | not serious | not serious | not serious | strong association | 87/7/8/0/0/8 (1.9%) | 87/7/8/0/0/8 (1.9%) | RR 1.08 (1.00-1.17) | All events (95% CI between 19 years to 73 more) | **B**\(\infty\) | LOW |

**Survival to discharge**

| 4 | observational studies | not serious | not serious | not serious | none | 52/154/3/2 (9.9%) | 62/65/3/4 (9.8%) | RR 1.09 (1.04-1.14) | 27 more per 1,000 (95% CI 12 48 events) | **B**\(\infty\) | LOW |

CI: Confidence interval; RR: Risk ratio.
Figure S4. Forest plot for pooling the effects of early (< 10 minutes vs. > 10 minutes) prehospital adrenaline administration on achievement of a CPC of 1-2.

CPC, cerebral performance category.
Figure S5. GRADE Assessment.

| No. of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Overall certainty | No. of patients | Effect | Certainty | Importance |
|---------------|--------------|--------------|---------------|--------------|-------------|---------------------|------------------|----------------|--------|-----------|------------|
| CPC-1-2       | randomized trials | not serious | not serious | not serious | not serious | very strong association | ** | NNT: 3.27 (CI: 1.79-6.26) | RR: 3.08 (CI: 2.21-4.29) | ** | CRITICAL |
| ROCC          | randomized trials | not serious | not serious | not serious | not serious | none | NNT: 5.05 (CI: 3.60-7.63) | RR: 3.20 (CI: 2.14-4.82) | ** | CRITICAL |
| Discharge     | randomized trials | not serious | not serious | not serious | not serious | very strong association | ** | NNT: 4.14 (CI: 2.73-6.26) | RR: 3.09 (CI: 2.19-4.36) | ** | CRITICAL |
| Admission     | randomized trials | not serious | not serious | not serious | not serious | none | NNT: 2.95 (CI: 2.32-3.75) | RR: 3.08 (CI: 2.25-4.28) | ** | CRITICAL |

CI: Confidence interval, RR: Risk ratio