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Review article

Adrenaline for out-of-hospital cardiac arrest resuscitation: A systematic review and meta-analysis of randomized controlled trials☆

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ABSTRACT

Introduction: The evidence for adrenaline in out-of-hospital cardiac arrest (OHCA) resuscitation is inconclusive. We systematically reviewed the efficacy of adrenaline for adult OHCA.
Methods: We searched in MEDLINE, EMBASE, and Cochrane Library from inception to July 2013 for randomized controlled trials (RCTs) evaluating standard dose adrenaline (SDA) to placebo, high dose adrenaline (HDA), or vasopressin (alone or combination) in adult OHCA patients. Meta-analyses were performed using random effects modeling. Subgroup analyses were performed stratified by cardiac rhythm and by number of drug doses. The primary outcome was survival to discharge and the secondary outcomes were return of spontaneous circulation (ROSC), survival to admission, and neurological outcome.
Results: Fourteen RCTs ($n = 12{,}246$) met inclusion criteria: one compared SDA to placebo ($n = 534$), six compared SDA to HDA ($n = 6174$), six compared SDA to an adrenaline/vasopressin combination ($n = 5202$), and one compared SDA to vasopressin alone ($n = 336$). There was no survival to discharge or neurological outcome differences in any comparison group, including subgroup analyses. SDA showed improved ROSC (RR 2.80, 95%CI 1.78–4.41, $p < 0.001$) and survival to admission (RR 1.95, 95%CI 1.34–2.84, $p < 0.001$) compared to placebo. SDA showed decreased ROSC (RR 0.85, 95%CI 0.75–0.97, $p = 0.02$; $I^2 = 48\%$) and survival to admission (RR 0.87, 95%CI 0.76–1.00, $p = 0.049$; $I^2 = 34\%$) compared to HDA. There were no differences in outcomes between SDA and vasopressin alone or in combination with adrenaline.
Conclusions: There was no benefit of adrenaline in survival to discharge or neurological outcomes. There were improved rates of survival to admission and ROSC with SDA over placebo and HDA over SDA.

Contents

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1. Introduction

Out-of-hospital cardiac arrest (OHCA) remains a significant cause of death worldwide. Despite advances in medical treatment, survival rates of OHCA remain low; the average survival rate in OHCA treated by emergency medical services (EMS) ranges from approximately 8 to 11%.[1–4] The routine administration of vasopressors, particularly adrenaline, has been a cornerstone of cardiac resuscitation for over 50 years and continues to be recommended by the recent update of the advanced life support guidelines.[5]

Adrenaline, also known as epinephrine, increases both aortic diastolic and coronary perfusion pressures during CPR, thus improving coronary blood flow during chest compressions.[6–8] Despite this, recent large observational studies have shown that the use of adrenaline in OHCA is associated with improved return of spontaneous circulation (ROSC) but not survival to hospital discharge and neurological outcome.[9,10] In fact, larger doses of adrenaline may be associated with decreased survival and worse neurological outcome.[10,11] Previously published systematic reviews did not include recently published randomized controlled trials (RCTs),[12–15] perform meta-analyses of included studies,[16] or evaluate the evidence for functional or neurological outcomes.[12,14] A recent systematic review and meta-analysis included both out-of-hospital and in-hospital cardiac arrests, and did not compare the use of adrenaline to other routinely used vasopressors (e.g. vasopressin) or evaluate adrenaline in specific patient subgroups (e.g. ventricular fibrillation, etc.).[17] Thus, there remains a lack of definitive evidence for the routine use of adrenaline.[18]

In 2010, the International Liaison Committee on Resuscitation (ILCOR) consensus of science statement identified the need for placebo-controlled trials to evaluate the routine use of vasopressors in OHCA.[19] In response to the paucity of trial evidence for the routine use of adrenaline, two RCTs attempted to compare the efficacy of adrenaline in out-of-hospital cardiac arrests against placebo or no drugs at all.[20,21] Both clinical trials demonstrated an increase in ROSC with the administration of adrenaline but no significant differences were observed in survival.[20,21] Moreover, both trials faced significant reluctance by EMS personnel to abandon traditional therapies and implement placebo in the intervention process resulting in underpowered trials.

In the absence of strong scientific basis, the historical standard prevails, which is to administer a standard dose of adrenaline of 1 mg every 3–5 min during advanced cardiac life support. In light of new clinical trial evidence,[20–24] we aimed to evaluate the cumulative trial evidence for the use of adrenaline in OHCA.

2. Objective

The objective of this study was to systematically review the efficacy of adrenaline in adult OHCA patients: standard dose adrenaline (SDA) compared to placebo, high dose adrenaline (HDA), adrenaline in combination with vasopressin (also known as antidiuretic hormone), or vasopressin alone.

3. Methods

3.1. Study selection

Both RCTs and quasi-RCTs that evaluated non-traumatic adult OHCAs treated by EMS personnel were included. Observational studies, commentaries, reviews, editorials and letters to the editor, which did not contain original data, and animal studies were excluded.

3.2. Interventions

Clinical trials that compared (1) SDA with placebo, (2) SDA with HDA (>1 mg per dose), (3) SDA with an adrenaline and vasopressin combination, and (4) SDA with vasopressin alone, by either intravenous or intraosseous administration, were included. SDA was defined as the administration of 1 mg of adrenaline. Adrenaline and vasopressin combination was defined as the use of both drugs concomitantly during resuscitation regardless of the order of drug administration or specific trial intervention. Studies whereby adrenaline was administered via an endotracheal tube or intracardiac route were excluded due to differences in dose, pharmacokinetics, and pharmacodynamics compared to intravenous drug administration.[25–27]

3.3. Outcomes

The primary outcome was survival to hospital discharge. Secondary outcomes were ROSC, survival to hospital admission, and

good neurological outcome at hospital discharge using a Cerebral Performance Category (CPC) of 1 or 2.[28,29]

3.4. Search strategy

We searched for English and non-English language studies in MEDLINE (January 1946 to July 1, 2013), EMBASE (1947 to July 1, 2013), EBM Reviews (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, and Health Technology Assessment) (up to July 1, 2013). The search terms included but were not limited to the following medical subject headings and keywords: "heart arrest", "ventricular fibrillation", "pulseless electrical activity", "asystole" with the Boolean operator 'and' combined with the following medical subject headings and keywords: "adrenaline", and "vasopressin" (Appendix 1). In addition, we hand-searched bibliographies of previous systematic reviews and the 2010 update of ILCOR Consensus Statement and Treatment Recommendations for advanced life support.[19] We also searched online resources such as BestBETS (http://www.bestbets.org/) and the first 200 hits of Google Scholar™. Ongoing clinical trials and unpublished studies were searched using the following sites: http://www.clinicaltrials.gov, http://www.controlledtrials.com, and http://www.centerwatch.com. Non-English titles, abstracts, and manuscripts were translated and evaluated for inclusion.

3.5. Data abstraction and analysis

Two independent reviewers (S.L. and J.D.W.) assessed the results of the literature search to identify eligible trials using a hierarchical selection of titles, abstracts, and then full manuscripts, as well as abstracted data from each included trial using a standardized data collection form. Primary study authors were contacted if further information regarding study inclusion, methodology, outcomes, or trial results was required. Two other independent reviewers (C.W.C. and L.J.M.), blinded to the names of authors and journals, assessed the risk of biases among selected trials based on recommendations by the Cochrane Collaboration[30] and the quality of evidence for each outcome as suggested by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[31,32] When consensus was not possible between reviewers, a third reviewer (P.S.S.) arbitrated. The data were analyzed using the Mantel-Haenszel random effects model with relative risk and 95% confidence intervals as effect measures. Statistical heterogeneity between clinical trials was assessed with the I^2 statistic. Cut-offs of $I^2 \leq 25\%$, I^2 within 26–50%, and $I^2 > 50\%$ were used to define low, moderate, and statistically significant heterogeneity, respectively.[33] Publication bias was evaluated using funnel plots and the Egger test. Analyses were performed using the Cochrane Review Manager software (RevMan, version 5.1.6).

3.6. Subgroup analyses

An a priori subgroup analysis was planned stratifying patients with ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT), pulseless electrical activity (PEA), and asystole. In addition, a separate a priori subgroup analysis was performed stratifying patients based on the number of intervention drug doses that was administered (or potentially administered) based on the study design of each clinical trial: (1) repeat-dose (>one dose) and (2) single-dose.

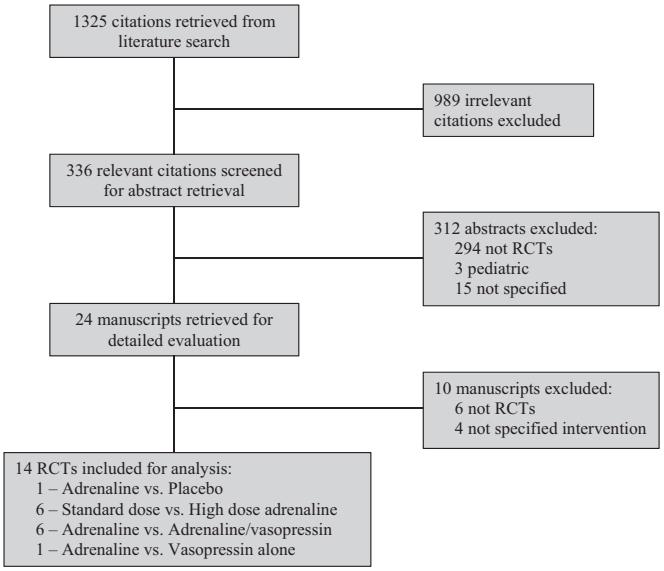


Fig. 1. Flowchart of study selection process.

4. Results

4.1. Characteristics of included studies

There were 1325 potential citations identified by the literature search after all duplicates were removed. Of these, 14 clinical trials were included and encompassed 12,246 patients (range, 40–3327 patients) in nine countries. The details of study selection including reasons for exclusion are outlined in Fig. 1 and Appendix 2. The kappa values ranged from 0.88 to 1.00 at the hierarchical selection of titles, abstracts and full manuscripts.

One trial ($n = 534$) compared SDA to placebo[21]; six trials ($n = 6174$) compared SDA to HDA, where HDA ranged from five to 15 times the dose of SDA[34–39]; six trials ($n = 5202$) compared SDA to adrenaline and vasopressin combination[22,24,40–43]; and one trial ($n = 336$) compared SDA to vasopressin alone.[23] The characteristics of the included studies are summarized in Table 1. Risk of bias assessment of the included trials is reported in Appendix 3. Overall, the GRADE quality of evidence was high for all outcomes of the SDA vs. HDA and SDA vs. adrenaline/vasopressin combination comparison groups. With only one trial for each comparison group, SDA vs. placebo[21] and SDA vs. vasopressin alone,[23] the quality of evidence was low for all outcomes in these comparison groups.

4.2. SDA vs. placebo

One trial ($n = 534$) compared SDA to placebo.[21] Patients who received SDA had higher rates of prehospital ROSC (RR 2.80, 95% CI 1.78–4.41, $p < 0.00001$) and survival to admission (RR 1.95, 95% CI 1.34–2.84, $p = 0.0004$) compared to those who received placebo. There were no significant differences in survival to discharge (RR 2.12, 95% CI 0.75–6.02, $p = 0.16$) and neurological outcome (RR 1.73, 95% CI 0.59–5.11, $p = 0.32$) between patients who received SDA compared to those who received placebo.

4.3. SDA vs. HDA

Six trials ($n = 6174$) compared SDA to HDA.[34–39] Meta-analysis showed decreased ROSC (RR 0.85; 95% CI 0.75–0.97, $p = 0.02$; $I^2 = 48\%$) and survival to admission (RR 0.87, 95% CI 0.76–1.00, $p = 0.049$; $I^2 = 34\%$) in the SDA group compared to HDA (Fig. 2).

Table 1
Study characteristics of included clinical trials.

	Location	Participants	Initial cardiac rhythms (%)	Witness status; bystander CPR (%)	Intervention groups	Intervention location
SDA vs. placebo						
Jacobs et al.[21]	Australia	Adult OHCAs ($N = 534$); age, mean $y \pm$ SD, 64 ± 18 (SDA) and 65 ± 17 (placebo)	VF/pVT 44 (SDA) and 48 (placebo), PEA 34 (SDA) and 27 (placebo), asystole 23 (SDA) and 25 (placebo)	Witnessed 54 (SDA) and 58 (placebo); bystander CPR 53 (SDA) and 49 (placebo)	Adrenaline 1 mg or placebo, up to 10 doses	Prehospital
SDA vs. HDA						
Brown et al.[34]	USA	Adult OHCAs ($N = 1280$); age, mean $y \pm$ SD, 66 ± 15 (SDA) and 66 ± 15 (HDA)	VF/pVT 50 (SDA) and 46 (HDA), PEA 18 (SDA) and 21 (HDA), asystole 32 (SDA) and 34 (HDA)	Witnessed 39 (SDA) and 36 (HDA), unwitnessed 61 (SDA) and 64 (HDA); bystander CPR 24 (SDA) and 23 (HDA)	Adrenaline 0.02 mg/kg (SDA) or 0.2 mg/kg (HDA), single dose	Prehospital
Callaham et al.[35]	USA	Adult OHCAs (N = 816); Age, mean $y \pm$ SD, 65 ± 19 (SDA) and 66 ± 18 (HDA)	VF/pVT 24, PEA 29, asystole 47 of total study population	Witnessed 63 (SDA) and 63 (HDA); Bystander CPR 22 (SDA) and 29 (HDA)	Adrenaline 1 mg (SDA) (n = 260), 15 mg (HDA) (n = 286) or NE 1 mg (n = 270), up to 3 doses	Prehospital
Choux et al.[36]	France	Adult OHCAs ($N = 536$); age, mean $y \pm$ SD, 62 ± 19 (SDA) and 59 ± 18 (HDA)	VF 16 (SDA) and 18 (HDA), PEA 9 (SDA) and 10 (HDA), asystole 75 (SDA) and 72 (HDA)	Not reported	Adrenaline, 1 mg (SDA) or 5 mg (HDA), up to 15 doses	Prehospital
Gueugniaud et al.[37]	France and Belgium	Adult OHCAs ($N = 3327$); age, mean $y \pm$ SD, 67 ± 15 (SDA) and 65 ± 15 (HDA)	VF 16 (SDA) and 18 (HDA), PEA 10 (SDA) and 10 (HDA), asystole 75 (SDA) and 73 (HDA)	Witnessed 79 (SDA) and 79 (HDA); bystander CPR: 9 (SDA) and 10 (HDA)	Adrenaline 1 mg (SDA) or 5 mg (HDA), up to 15 doses	Prehospital
Sherman et al.[38]	USA	Adult OHCAs ($N = 140$); age, mean $y \pm$ SD, 68 ± 14 (SDA) and 65 ± 14 (HDA)	VF 16 (SDA) and 31 (HDA), asystole 84 (SDA) and 69 (HDA)	Witnessed 74 (SDA) and 59 (HDA); Bystander CPR rates not reported	Adrenaline, 0.01 mg/kg (SDA) or 0.1 mg/kg (HDA), up to 4 doses	Emergency department
Stiell et al.[39]	Canada	Adult OHCAs ($n = 335$) and in-hospital cardiac arrests ($n = 315$); age, mean $y \pm$ SD, 67 ± 15 (SDA) and 66 ± 15 (HDA)	Not reported in OHCA patients	Not reported in OHCA patients	Adrenaline 1 mg (SDA) or 7 mg (HDA), up to 5 doses	Emergency department
SDA vs. adrenaline/vasopressin						
Callaway et al.[40]	USA	Adult OHCAs ($N = 325$); age, mean $y \pm$ SD, 65 ± 17 (SDA) and 66 ± 17 (Adr/Vaso)	VF/AED shock 26 (SDA) and 29 (Adr/Vaso), PEA 23 (SDA) and 22 (Adr/Vaso), asystole 51 (SDA) and 50 (Adr/Vaso)	Witnessed 55 (SDA) and 48 (Adr/Vaso); Bystander CPR: 35 (SDA) and 31 (Adr/Vaso)	Vasopressin 40 IU or placebo after initial dose of adrenaline (unblinded), single dose	Prehospital
Ducros et al.[24]	France	Adult OHCAs ($N = 44$); age, mean $y \pm$ SE, 60 ± 4 (SDA) and 56 ± 4 (Adr/Vaso)	VF 0 (SDA) and 14 (Adr/Vaso), PEA 50 (SDA) and 21 (Adr/Vaso), asystole 50 (SDA) and 64 (Adr/Vaso)	All OHCA were witnessed and received CPR by firefighters prior to EMS arrival	Adrenaline 1 mg (unblinded) followed by vasopressin 40IU + placebo or vasopressing 40 IU + nitroglycerin 300 μg, up to 3 doses	Prehospital
Gueugniaud et al.[41]	France	Adult OHCAs ($N = 2894$); age, mean $y \pm$ SD, 62 ± 15 (SDA) and 61 ± 15 (Adr/Vaso)	VF 9 (SDA) and 9 (Adr/Vaso), PEA 8 (SDA) and 8 (Adr/Vaso), asystole 82 (SDA) and 83 (Adr/Vaso)	Witnessed 76 (SDA) and 74 (Adr/Vaso); Bystander CPR 26 (SDA) and 28 (Adr/Vaso)	Adrenaline 1 mg + placebo or adrenaline 1 mg + vasopressin 40 IU, up to 2 doses	Prehospital
Lindner et al.[42]	Germany	Adult OHCAs ($N = 40$); Age, mean $y \pm$ SE, 66 ± 4 (SDA) and 64 ± 3 (Adr/Vaso)	VF only	Witnessed 60 (SDA) and 65 (Adr/Vaso); Bystander CPR 25 (Adr) and 20 (Adr/Vaso)	Adrenaline 1 mg or vasopressin 40 IU, single dose	Prehospital
Ong et al.[22]	Singapore	Adult OHCAs ($N = 727$); age, mean $y \pm$ SD, 65 ± 15 (SDA) and 65 ± 14 (Adr/Vaso)	VF/pVT 9 (SDA) and 7 (Adr/Vaso), PEA 20 (SDA) and 18 (Adr/Vaso), asystole 67 (SDA) and 71 (Adr/Vaso)	Witnessed 75 (SDA) and 71 (Adr/Vaso); Bystander CPR 14 (SDA) and 17 (Adr/Vaso)	Adrenaline 1 mg or vasopressin 40 IU, single dose	Emergency department
Wenzel et al.[43]	Austria, Germany and Switzerland	Adult OHCA ($N = 1186$); age, mean $y \pm$ SD, 66 ± 14 (SDA) and 67 ± 14 (Adr/Vaso)	VF 42 (SDA) and 38 (Adr/Vaso), PEA 14 (SDA) and 18 (Adr/Vaso), asystole 45 (SDA) and 45 (Adr/Vaso)	Witnessed 80 (SDA) and 77 (Adr/Vaso); bystander CPR 18 (SDA) and 19 (Adr/Vaso)	Adrenaline 1 mg or vasopressin 40 IU, up to two doses	Emergency department
SDA vs. vasopressin						
Mukoyama et al.[23]	Japan	Adult OHCAs ($N = 336$); age, mean $y \pm$ SD, 64 ± 19 (SDA) and 67 ± 15 (Vaso)	VF 25 (SDA) and 23 (Vaso), PEA 14 (SDA) and 15 (Vaso), asystole 61 (SDA) and 62% (Vaso)	Witnessed 46 (SDA) and 43 (Vaso); Bystander CPR 17 (SDA) and 14 (Vaso)	Adrenaline 1 mg or vasopressin 40 IU, up to 4 doses	Emergency department

OHCA: out-of-hospital; SDA: standard-dose adrenaline; HDA: high-dose adrenaline; VF: ventricular fibrillation; pVT: pulseless ventricular tachycardia; PEA: pulseless electrical activity; Adr/Vaso: adrenaline/vasopressin combination; Vaso: vasopressin alone.

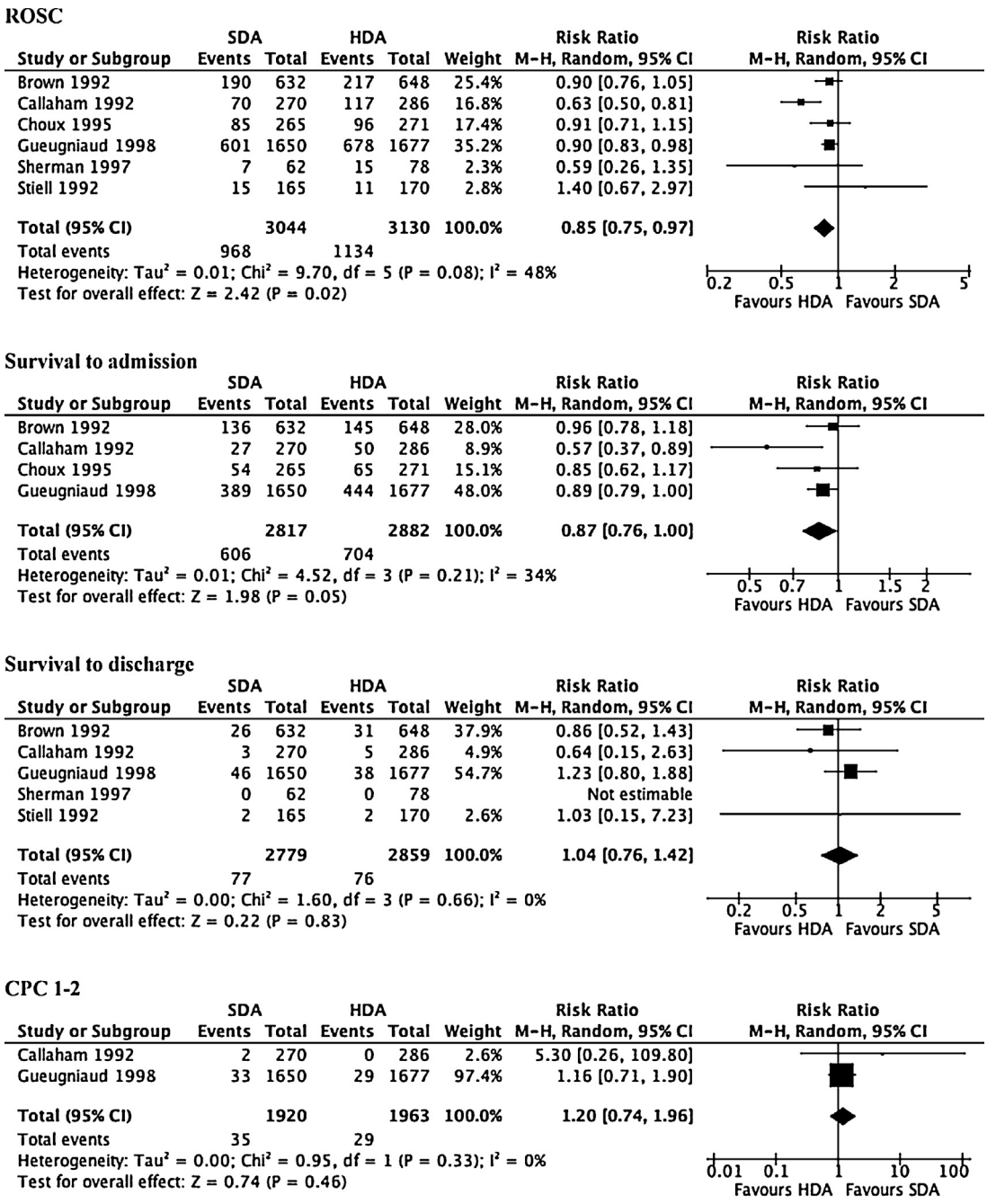


Fig. 2. Summarized results between SDA vs. HDA on patient outcomes.

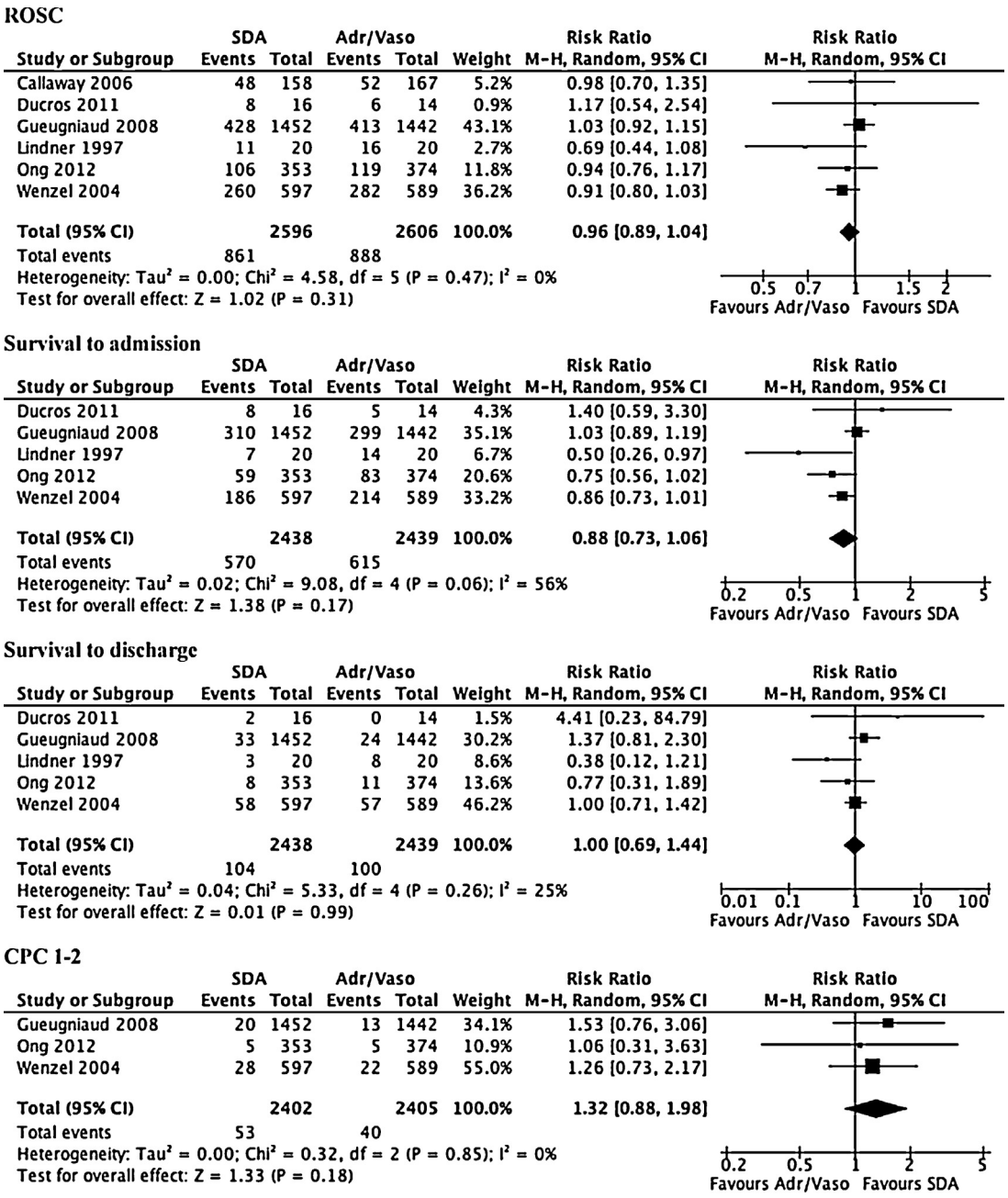
There were no differences in survival to discharge (RR 1.04, 95% CI 0.76–1.42, $p = 0.83$; $I^2 = 0\%$) and neurological outcome (RR 1.20, 95% CI 0.74–1.96, $p = 0.46$; $I^2 = 0\%$) between SDA and HDA (Fig. 2).

4.4. SDA vs. adrenaline/vasopressin

Six trials ($n = 5202$) compared SDA to adrenaline and vasopressin combination.[22,24,40–43] There were no differences in ROSC (RR 0.96, 95% CI 0.89–1.04, $p = 0.31$; $I^2 = 0\%$), survival to admission (RR 0.88, 95% CI 0.73–1.06, $p = 0.17$; $I^2 = 56\%$), survival to discharge (RR 1.00, 95% CI 0.69–1.44, $p = 0.99$; $I^2 = 25\%$), and neurological outcome (RR 1.32, 95% CI 0.88–1.98, $p = 0.18$; $I^2 = 0\%$) among patients who were treated with SDA compared to adrenaline/vasopressin (Fig. 3).

4.5. SDA vs. vasopressin alone

One trial ($n = 336$) compared SDA to vasopressin alone.[23] There were no differences in ROSC (RR 0.93, 95% CI 0.66–1.31, $p = 0.67$), survival to discharge (RR 0.68, 95% CI 0.25–1.82, $p = 0.44$), and neurological outcome (RR 0.68, 95% CI 0.25–1.82, $p = 0.44$) between patients who received SDA compared to vasopressin alone. Survival to admission was not assessed in this trial.



SDA=standard dose adrenaline, Adr/Vaso=adrenaline/vasopressin combination, CPC=Cerebral Performance Category, ROSC=return of spontaneous circulation#

Fig. 3. Summarized results between SDA vs. adrenaline/vasopressin on patient outcomes.

4.6. Subgroup analyses

4.6.1. Initial cardiac rhythm

In the single trial comparing SDA to placebo, patients were stratified by shockable and non-shockable rhythms.[21] There were improved rates of prehospital ROSC and survival to admission in patients who received SDA with either shockable or non-shockable rhythms compared to placebo; however, there was no difference in survival to discharge between both groups. There were no data on neurological outcomes stratified by cardiac rhythm.

When comparing SDA to HDA stratified by initial rhythm, there was one trial that provided sufficient data on ROSC, survival to admission and survival to discharge,[37] and one trial that provided data on ROSC and survival to discharge.[38] No trials provided neurological outcomes. There were no differences in survival to discharge when stratified by cardiac rhythm. Patients presenting in asystole or PEA showed lower ROSC (RR 0.78, 95% CI 0.65–0.94, $p = 0.009$; $I^2 = 49\%$) and survival to admission (RR 0.81, 95% CI 0.70–0.93, $p = 0.004$), respectively, with SDA compared to HDA (Appendix 4).

When comparing SDA to adrenaline/vasopressin, there were three trials that had sufficient data on ROSC, survival to admission and survival to discharge outcomes,[22,41,43] and one trial provided data on ROSC.[40] No trials provided neurological outcome data stratified by cardiac rhythm. There were no differences in ROSC, survival

to admission, and survival to discharge when comparing SDA to adrenaline/vasopressin in patients stratified by cardiac rhythm (Appendix 5).

In the single trial comparing SDA to vasopressin alone, patients were stratified by VF and non-VF rhythms.[23] There were no differences between SDA compared to vasopressin alone[23] for ROSC, survival to discharge, and neurological outcome, stratified by cardiac rhythm.

4.6.2. Repeat-dose vs. single-dose intervention

There were five trials that compared SDA to HDA in repeated doses,[35–39] with two trials using up to 15 doses of intervention drug.[36,37] There were no differences in ROSC (RR 0.83, 95% CI 0.68–1.01, $p = 0.06$; $I^2 = 58\%$), survival to admission (RR 0.81, 95% CI 0.66–1.01, $p = 0.06$; $I^2 = 46\%$), survival to discharge (RR 1.16, 95% CI 0.78–1.73, $p = 0.47$; $I^2 = 0\%$), and neurological outcome (RR 1.20, 95% CI 0.74–1.96, $p = 0.46$; $I^2 = 0\%$), of repeat-dose SDA to repeat-dose HDA (Appendix 6). There was only one trial that compared single-dose SDA to single dose HDA and it found no differences in ROSC, survival to admission and survival to discharge.[34]

There were three trials that compared SDA to adrenaline/vasopressin in repeated doses[24,41,43] and three trials that compared SDA to adrenaline/vasopressin in single dose.[22,40,42] There were no differences in ROSC (RR 0.97, 95% CI 0.89–1.07, $p = 0.59$; $I^2 = 13\%$), survival to admission (RR 0.96, 95% CI 0.81–1.13, $p = 0.61$; $I^2 = 45\%$), survival to discharge (RR 1.12, 95% CI 0.84–1.49, $p = 0.45$; $I^2 = 0\%$), and neurological outcome (RR 1.35, 95% CI 0.88–2.08, $p = 0.17$; $I^2 = 0\%$) when comparing repeat-dose SDA to repeat-dose adrenaline/vasopressin (Appendix 7). When comparing single-dose SDA to single-dose adrenaline/vasopressin, there were no differences in ROSC, survival to discharge, and neurological outcome. However, there was decreased survival to admission with single-dose SDA compared to single-dose adrenaline/vasopressin (RR 0.68, 95% CI 0.49–0.96, $p = 0.03$; $I^2 = 19\%$) (Appendix 8).

5. Discussion

In this systematic review and meta-analysis, we evaluated the cumulative trial evidence on the efficacy of adrenaline during OHCA resuscitation. To our knowledge, recent systematic reviews have not attempted to perform a comprehensive meta-analysis on standard recommended doses of adrenaline for OHCA compared with different pharmacological interventions.[16,17] There were no differences in survival to discharge or neurological outcomes at discharge when OHCA patients received SDA compared to placebo, HDA, adrenaline and vasopressin, or vasopressin alone, which is consistent with previous systematic reviews and meta-analyses.[13,15,16,44,45] There was, however, an advantage of SDA over placebo and HDA over SDA in overall survival to admission and ROSC, which is also consistent with previous reviews.[15,16]

So why is there no difference in the rate of survival to discharge when there are increased rates of ROSC and survival to admission in patients who receive adrenaline? In a recent prospective, observational study of over 400,000 Japanese patients using a propensity-matched analysis, Hagihara et al. reported increased ROSC but decreased one month survival in patients who received adrenaline compared to those who did not.[10] This was thought to be due to the short-term benefits of adrenaline in improving coronary blood flow at the expense of other organs due to its potent vasoconstrictive effects.[6–8] These findings may also be due to differences in in-hospital therapies after hospital admission between study groups, which are often not reported or difficult to control for.[10,21–24,34–43] Moreover, many of the included trials[34–39,42,43] were published prior to the routine use of targeted temperature management[46–49] and percutaneous coronary intervention[47,48] in the post-resuscitation period. Future trials should report in-hospital therapies to address these potential confounders.

In contrast, in the single trial that compared SDA to placebo in this systematic review, there was neither benefit nor harm to SDA in survival to discharge or good neurological outcome.[21] This was the first randomized, multi-centered, placebo-controlled trial powered to detect a survival difference but despite receiving appropriate research ethics board approval, several ambulance services refused participation due to perceived ethical and political pressures. Subsequently, this resistance resulted in an early termination of the study and was ultimately underpowered to detect a survival difference.[21] Olasveengen et al. performed a similarly well-designed trial comparing patients who received intravenous access for drug administration during resuscitation by paramedics and patients who were not given intravenous access.[20] They also found no differences in survival to discharge or neurological outcomes, but patients with intravenous access showed improved survival to admission and ROSC.[20] Although this trial did not meet our selection criteria, we performed a post hoc sensitivity analysis to include this trial in a pooled analysis with the RCT by Jacobs et al.[21] (data not shown), which was not significantly different compared to our primary analysis.

In our subgroup analysis stratified by initial cardiac arrest rhythms, there was no survival to discharge advantage in any of the comparison groups. However, despite the few trials that provided cardiac rhythm data, patients presenting in asystole or PEA showed lower ROSC and survival to admission, respectively, with SDA compared to HDA (Appendix 4). These results are hypothesis-generating and may suggest that these patients require increased peripheral vasoconstriction and higher coronary perfusion pressures as their etiology of their cardiac arrest may differ significantly compared to patients with VF or VT. In a separate subgroup analysis, we also found that repeat-dose SDA trended toward lower rates of survival to admission and ROSC, but not survival to discharge, compared to repeat-dose HDA (Appendix 6). This subgroup analysis may again reflect the short-term benefits of adrenaline in improving coronary blood flow without any long-term survival benefit.[11]

The lack of efficacy and effectiveness of adrenaline may be confounded by the quality of CPR during cardiac arrest, which has been demonstrated in animal models.[50] CPR quality was not measured or reported in the included RCTs, which limited the interpretation of these individual trials and of our results. Future trials evaluating adrenaline should measure and report CPR quality (rate, depth, compression fraction, etc.) to ensure adequate interpretation of their results.

This was the first comprehensive systematic review and meta-analysis of adrenaline for OHCA with multiple comparison groups and multiple subgroup analyses based on patient and intervention characteristics. We employed the Cochrane Collaboration tool[30] and GRADE criteria[31,32] to assess the risk of biases in our included studies and followed the PRISMA guidelines for reporting.[51] This review, however, had several limitations. First, our meta-analysis was limited by the small number of studies in each of the comparison groups, which limits our power to interpret the comparisons for all outcomes and our ability to test for the risk of publication bias. Second, two trials[37,41] contributed approximately half of the patients in the meta-analysis. Our results, however, were consistent across multiple studies and we also chose to use random-effects models, which may give a higher weight to large studies but have lower large to small study gradient in weight than fixed effects models when there is significant variation across studies. Third, all included trials in the SDA vs. HDA analysis were published prior to 2000,[34–39] and since that time, resuscitation guidelines have

substantially changed in regards to chest compression ratios and an increased focus on chest compression quality. This may limit our interpretation of these results and the use of SDA compared to HDA in current resuscitation practices. Fourth, individual studies may have had unmeasured confounders, such as patient-specific characteristics (e.g. co-morbidities, arrest duration), situational characteristics (e.g. arrest location, witness status, bystander CPR, CPR quality, EMS response times), and interventions performed in the prehospital and in-hospital settings.[52,53] We attempted to address the heterogeneity between studies by using random effects models and several subgroup analyses. Lastly, the treatment of cardiac arrest, particularly the increased emphasis of chest compressions over ventilation in CPR and the increased practice of routine targeted temperature management and percutaneous coronary intervention, has changed over time, which may limit our interpretation of the results about the role of adrenaline in OHCA.

The evidence for the routine use of adrenaline is perceived to be at equipoise within the international community of resuscitation scientists requiring re-evaluation[19] as suggested by this comprehensive systematic review and meta-analysis. There is a need for well-designed, placebo-controlled, and adequately powered RCTs to evaluate the efficacy of adrenaline and to determine its optimal dosing.[11,16,54] The question as to the efficacy of adrenaline for OHCA remains unanswered.

6. Conclusions

There was no clear advantage of SDA over placebo, HDA, adrenaline and vasopressin combination, or vasopressin alone, in survival to discharge or neurological outcomes after OHCA. There were improvements in rates of survival to admission and ROSC with HDA over SDA and with SDA over placebo. Thus, the efficacy of vasopressor use in OHCA remains unanswered. Future trials are needed to determine the optimal dose of adrenaline for OHCA.

Conflict of interest statement

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Appendix A. Supplementary data

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