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Review

Vasopressors during adult cardiac arrest: A systematic review and meta-analysis

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Abstract

Aim: To systematically review the literature on the use of vasopressors during adult cardiac arrest to inform an update of international guidelines.

Methods: PRISMA guidelines were followed. We searched Medline, Embase, Web of Science, CINAHL, and the Cochrane Library for controlled trials and observational studies. The population included adults with cardiac arrest in any setting. Pairs of investigators reviewed studies for relevance, extracted data, and assessed the risk of bias for individual studies. Certainty of evidence was evaluated using GRADE for controlled trials and meta-analyses were performed when at least two studies could be pooled.

Results: We included 15 controlled trials and 67 observational studies. The majority of studies included out-of-hospital cardiac arrest only. Meta-analyses were performed for two controlled trials comparing epinephrine to placebo, three comparing vasopressin to epinephrine, and three comparing epinephrine plus vasopressin to epinephrine only. All controlled trials ranged between low to some concern in risk of bias. The certainty of evidence ranged from very low to high. Risk of bias for observational studies was generally critical or serious, largely due to confounding and selection bias.

Conclusions: Controlled trial data suggest that epinephrine improves return of spontaneous circulation, survival to hospital discharge, and 3-month survival in out-of-hospital cardiac arrest. The improvement in short-term outcomes appeared more pronounced for non-shockable rhythms.

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Differences in long-term neurological outcome did not reach statistical significance, although there was a signal toward improved outcomes. Controlled trial data indicated no benefit from vasopressin with or without epinephrine compared to epinephrine only.
Keywords: ILCOR, Vasopressor, Epinephrine, Cardiac arrest, Advanced life support, Systematic review, Meta-analysis

Introduction

Cardiopulmonary arrest is a major contributor to morbidity and mortality worldwide.[1] Beyond rapid defibrillation for shockable rhythms and early initiation of effective chest compressions, there are few therapies that have reliably shown to improve outcomes for cardiac arrest patients. Vasopressor therapy for cardiac arrest was first introduced in a series of dog experiments in 1903[2,3] and later in the 1960s.[4] These animal-based studies eventually gave way to widespread usage in human cardiac arrest despite lack of randomized data in humans at the time. The American Heart Association (AHA) and European Resuscitation Council (ERC) have included the use of vasopressors in their cardiac arrest resuscitation algorithms since the inception of their guidelines.[5,6] Despite the common and widespread use of vasopressor agents during cardiopulmonary resuscitation, the evidence base supporting their effectiveness is still evolving.

In a 2015 review of existing science published by the International Liaison Committee on Resuscitation (ILCOR), the administration of standard-dose epinephrine (1 mg bolus dose) during cardiopulmonary resuscitation was given a weak recommendation supported by only very-low quality evidence.[7] The administration of vasopressin, the combination of epinephrine and vasopressin, and the administration of high-dose epinephrine ($\geq$0.2 mg/kg or 5 mg bolus dose) were not recommended as there was no evidence to suggest a benefit over standard-dose epinephrine. For medication timing, when standard-dose epinephrine is given during cardiopulmonary resuscitation for patients with non-shockable rhythms, a weak recommendation based on low-quality evidence was made to administer the epinephrine as soon as possible.[7]

Since the 2015 review of vasopressors, a large randomized trial comparing epinephrine to placebo for out-of-hospital cardiac arrest (OHCA) has been published.[8] This study, along with other recent work, prompted ILCOR to commission a systematic review and meta-analysis of vasopressors during cardiac arrest to inform an updated Consensus on Science and Treatment Recommendation (CoSTR). The incorporation of this updated data into the existing body of evidence is crucial for the development of future guidelines of the administration of vasopressors during cardiac arrest. In the present study, we report the results of a systematic review and meta-analysis of vasopressors in cardiac arrest.

Methods

Protocol and registration

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] The PRISMA checklist is provided in the Supplemental Content. The protocol was prospectively registered at the International Prospective Registry of Systematic Reviews (PROSPERO no. CRD42018116989). The protocol is provided in the Supplemental Content. The systematic review was commissioned by ILCOR.

Eligibility criteria and outcomes

We used the PICO format (Population, Intervention, Comparison, Outcome) to frame the study question: in adults (>18 years) in any setting (in-hospital or out-of-hospital) with cardiac arrest from any etiology (P), does intravenous or intraosseous administration of a vasopressor or combination of vasopressors (I), as compared to a different vasopressor, combination of vasopressors, or no vasopressor (C) change outcomes (O).

Outcomes were prioritized by the ILCOR Advanced Life Support task force (see Supplemental Content for rankings). These outcomes included short-term survival (return of spontaneous circulation (ROSC) and survival to hospital admission), mid-term survival (survival to hospital discharge, 28 days, 30 days, or 1 month), mid-term favorable neurological outcomes (Cerebral Performance Category score of 1–2 or modified Rankin Scale 0–3 at hospital discharge, 28 days, 30 days, or 1 month) and long-term outcomes (after 1 month). For randomized clinical trials, we also included poor neurological outcome (modified Rankin Score 4–5) at 3 months or longer.

Randomized controlled trials, non-randomized controlled trials, and observational studies (cohort and case-control studies) with a comparison group were included. Studies comparing different doses or timing of vasopressors were also included. Studies on the combination of vasopressin and steroids were not included as steroids were determined not to fall within the category of vasopressors. Animal studies, ecological studies, case series, case reports, reviews, abstracts, editorials, comments, and letters to the editor were not included. Studies with fewer than 10 patients in either group and studies without quantitative results were excluded. There were no limitations on publication period or manuscript language (provided there was an English abstract). Given the number of human randomized trials comparing high-dose epinephrine to standard-dose epinephrine, observational studies specifically comparing high-dose to standard-dose epinephrine were not included. Additionally, because ILCOR performed a similar systematic review in 2015[7] inclusive of the high-dose vs standard-dose epinephrine studies, the Advanced Life Support task force determined *a priori* that this subset of controlled trials would not be re-analyzed unless new controlled trials published since the 2015 review were identified.

Information sources and search strategy

We searched the following electronic bibliographic databases on November 23, 2018: Medline, Embase, Web of Science, CINAHL, and the Cochrane Library. The search terms were developed in collaboration with a research librarian. The bibliographies of included articles were reviewed for potential additional articles. Ongoing trials on vasopressor therapy were identified via a search of the International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/), which occurred on January 24, 2019. The search strategy for each database and the International Clinical Trials Registry Platform can be found in the Supplemental Content.

Study selection

Pairs of reviewers, using pre-defined screening criteria, independently screened all titles and abstracts retrieved by the systematic search. Kappa statistics were calculated to assess inter-rater agreement. An *a priori* decision was made to have a third reviewer screen all the excluded titles and abstracts to ensure optimal capture of relevant articles if the Kappa was less than 0.60. The reviewers were blinded to author and journal names during the screening stage. Any discrepancies regarding inclusion and exclusion of articles were resolved by discussion between the two reviewers, and remaining discrepancies adjudicated by a third reviewer. Those articles retained for full-text assessment were then reviewed in duplicate and a final set of full-text reports was identified for data abstraction. Any disagreement regarding eligibility was resolved by discussion.

Data collection and data items

Using a predefined data abstraction tool, data pertinent to the PICO were abstracted by pairs of reviewers with any missing statistical parameters calculated from provided data if permitted. Any discrepancies in the extracted data were identified and resolved via discussion and consensus. The data abstraction tool can be found in the Supplemental Content.

Risk of bias in individual studies

For each included study, two authors independently reviewed the risk of bias and any disagreements were resolved by discussion between these authors. The revised Cochrane risk-of-bias tool was used for controlled trials[10] and the ROBINS-I tool was used for observational studies.[11] In most cases bias was assessed per comparison rather than per outcome, since there were no meaningful differences in bias across outcomes. In cases where differences in risk of bias existed between outcomes this was noted.

Data synthesis and confidence in cumulative evidence

Studies were assessed for clinical, methodological, and statistical heterogeneity when appropriate.[9] Meta-analyses were performed for selected controlled trials comparing epinephrine to placebo (no epinephrine), initial vasopressin to epinephrine, and initial epinephrine plus vasopressin to epinephrine only. When data were deemed too heterogeneous or biased to allow for meaningful meta-analysis, we provided a narrative synthesis of the results.

Treatment effects across studies were pooled using Mantel-Haenszel statistics with a fixed-effects model or random-effects model, depending on the heterogeneity of the data. Effect measures are reported as relative risk ratios (RR) and absolute risk differences, with 95% confidence intervals. Additional prespecified meta-analyses were performed for subgroups of patients based on initial rhythm (shockable or non-shockable rhythm). Review Manager version 5.0 (The Cochrane Collaboration, 2014) was used to perform meta-analyses of the study data for each outcome. Complete details of the data synthesis process can be found in the protocol.

The certainty of the overall evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology ranging from very low certainty of evidence to high certainty of evidence.[12] Detailed assessment of overall risk of bias, inconsistency, indirectness, imprecision and potential other issues such as publication bias were tabulated.

Results

Study selection

The search strategy identified 4142 unique records, of which 3938 records were excluded based on review of titles and abstracts. The Kappa for the initial screening was 0.55, prompting review by a third investigator. Of the 204 full-text articles reviewed, 115 were excluded (Kappa = 0.81) for the reasons listed in Fig. 1. One additional article was identified after review of bibliographies, with a total of 89 articles included.[8,13–100] We were not able to formally assess publication bias as outlined in the protocol due to the low number of studies included for each meta-analysis.

Overview of randomized controlled trials

A total of 22 controlled trials were identified.[8,13–33] Eight of these trials compared high-dose epinephrine to standard-dose epinephrine,[13–20], of which one trial also compared norepinephrine to standard-dose epinephrine.[20] High-dose epinephrine was reviewed in detail by the previous ILCOR-commissioned systematic review and no new studies since that review were identified.[7] Fifteen controlled trials were therefore included, published between 1985 and 2018.[8,20–33] Two of the trials compared the use of epinephrine to placebo,[8,21] nine trials compared the use of vasopressin or the combination of vasopressin and epinephrine to epinephrine,[22–30] three trials compared epinephrine to another vasopressor,[20,31,32] and one trial compared the use of intravenous drugs to no intravenous drugs during cardiac arrest.[33] The trials included between 30 and 8014 patients and seven trials included more than 500 patients. Trials were conducted in Europe (n = 8), North America (n = 3), Asia (n = 3), and Australia (n = 1). Thirteen trials included patients with OHCA, one included patients with in-hospital cardiac arrest (IHCA),[22] and one trial included patients with cardiac arrest in both settings.[23] All trials were described as including only adult patients. One of these included ages 15 and above[31] and three included ages 16 and above.[8,22,23] Due to the apparent very small number of patients in these studies under the age of 18, and the difficulty of separating those few patients out, the decision was made to include those studies. A brief overview of the trials is provided in Table 1 and additional details are provided in the Supplemental Content.

An overview of the bias assessments is provided in Table 2, while details of the approach are provided in the Supplemental Content. Overall, three trials were rated as a high risk of bias, ten were rated as having some concerns for risk of bias, and the remaining trials were rated as having a low risk of bias. Risk of bias was primarily related to concerns with the randomization process and deviations from the intended intervention.

Overview of observational studies

Sixty-seven observational studies were included.[34–100] Fifty-two studies compared the use of one vasopressor or a combination of

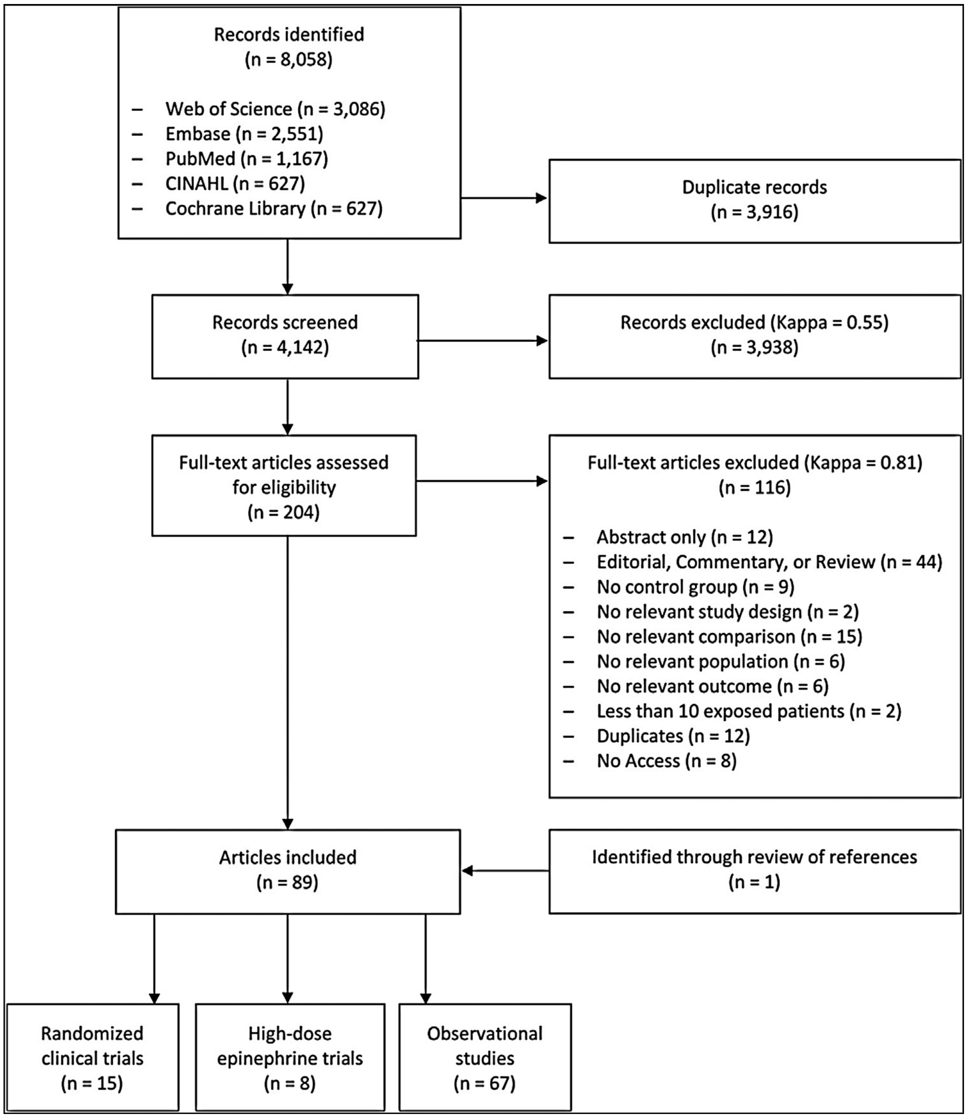

Fig. 1 – PRISMA diagram.
Diagram illustrating the selection of articles during the review process. Out of 4142 screened records, 204 full-text articles were assessed for eligibility, and 89 studies were included. Of the included studies, 15 were randomized clinical trials, 8 were trials comparing high-dose epinephrine to standard-dose epinephrine, and 67 were observational studies. One randomized clinical trial included high-dose epinephrine, standard-dose epinephrine, and norepinephrine arms, and was therefore counted twice.

vasopressors to no vasopressor, another vasopressor, or a combination of vasopressors.[34–85] Sixteen studies addressed the timing of vasopressors[84–99] and one study addressed the dosing of vasopressors during cardiac arrest.[100] Two of the studies included both direct comparisons of vasopressors and timing.[84,85] The 52 comparative studies were published between 1993 and 2018. Studies were based in Asia (n = 26), Europe (n = 14), North America (n = 10), South America (n = 1), and Australia (n = 1). The majority of studies were in OHCA (n = 43), while the remaining were in IHCA (n = 6) or either setting (n = 3). Studies related to the timing of vasopressors were published from 2012 to 2018 and were either based in North America (n = 10) or Asia (n = 6). Twelve of the timing studies included patients with OHCA, while four studies included patients with IHCA. Additional details on individual studies including results are provided in the Supplemental Content. The single included study comparing two different vasopressor doses was from North America, published in 2018.[100]

Details on the risk of bias for individual studies are provided in the Supplemental Content, including a summary of the criteria for attributing risk of bias in each domain. For the 52 comparative studies, the risk of bias was rated as critical for the majority of studies and as serious in five studies (4 in OHCA and 1 in IHCA), primarily due to concerns regarding confounding or selection bias. For the studies related to timing of vasopressors, all studies were rated as having a critical risk of bias, also largely due to confounding and/or selection bias. The high degree of heterogeneity across studies and the serious to critical risk of bias precluded any meaningful meta-analyses for the observational studies.

Table 1 – Overview of controlled trials.

Study	Country	Years of inclusion	Intervention	Comparator	Survival to hospital discharge	
					Intervention	Comparator
Perkins et al., 2018[8]	UK	2014–2017	Epinephrine	Placebo	128/4009 (3.2)	91/3995 (2.3)
Jacobs et al., 2011[21]	Australia	2006–2009	Epinephrine	Placebo	11/272 (4.0)	5/262 (1.9)
Olasveengen et al., 2009[33]	Norway	2003–2008	IV drug administration	No IV drug administration	44/418 (10.5)	40/433 (9.2)
Mukoyama et al., 2009[29]	Japan	2005	Vasopressin	Epinephrine	10/178 (5.6)	6/158 (3.8)
Lindner et al., 1997[28]	Germany	1994–1995	Vasopressin	Epinephrine	8/20 (40)	3/20 (15)
Stiell[a] et al., 2001[22]	Canada	1997–1998	Vasopressin	Epinephrine	12/104 (11.5)	13/96 (13.5)
Wenzel et al., 2004[30]	Austria, Germany, and Switzerland	1999–2002	Vasopressin	Epinephrine	57/578 (9.9)	58/588 (9.9)
Ong[b] et al., 2012[23]	Singapore	2006–2009	Vasopressin	Epinephrine	11/374 (2.9)	8/353 (2.3)
Ghafourian et al., 2015[24]	Iran	2013	Epinephrine plus vasopressin	Epinephrine only	8/50 (16)	5/50 (10)
Gueugniaud et al., 2008[27]	France	2004–2006	Epinephrine plus vasopressin	Epinephrine only	24/1439 (1.7)	33/1448 (2.3)
Ducros et al., 2011[26]	France	2001–2004	Epinephrine plus vasopressin	Epinephrine only	0/14 (0)	2/16 (12.5)
Callaway et al., 2006[25]	USA	2003–2005	Epinephrine plus Vasopressin	Epinephrine only	5/167 (3.0)	4/158 (2.5)
Silfvast et al., 1985[31]	Finland	1983–1984	Phenylephrine	Epinephrine	NR	NR
Lindner et al., 1991[32]	Germany	NR	Norepinephrine	Epinephrine	6/25 (24)	4/25 (16)
Callaham et al., 1992[20]	USA	1990–1992	Norepinephrine	Epinephrine	7/260 (2.7)	3/270 (1.1)

UK: United Kingdom, USA: United States of America, NR: Not reported, IV: Intravenous. Several studies, including Perkins et al., allowed for either intravenous or intraosseous administration of study drug, and direct comparison of route of administration was not done.

[a] Only including in-hospital cardiac arrest patients.

[b] Including both out-of-hospital and in-hospital cardiac arrest patients.

Table 2 – Risk of bias for controlled trials.

Study	Domain					
	Randomization	Deviation from intended intervention	Missing outcome	Measurement of outcome	Selective reporting	Overall
Perkins et al., 2018[8]	Low	Low	Some concern[a] Low	Low	Low	Some concern[a]
Jacobs et al., 2011[21]	Low	Low	Low	Low	Low	Low
Olasveengen et al., 2009[33]	Low	High[b]	Low	Some concern[c]	Low	High
Mukoyama et al., 2009[29]	Some concern[d]	Some concern[e]	Low	Low	Some concern[f]	Some concern
Lindner et al., 1997[28]	Low	Low	Low	Some concern[c]	Some concern[f]	Some concern
Stiell et al., 2001[22]	Some concern[g]	Low	Low	Low	Some concern[f]	Some concern
Wenzel et al., 2004[30]	Low	Low	Low	Low	Some concern[f]	Some concern
Ong et al., 2012[23]	Some concern[h]	Low	Low	Low	Low	Some concern
Ghafourian et al., 2015[24]	High[i]	Some concern[j]	Low	Low	High[k]	High
Gueugniaud et al., 2008[27]	Low	Low	Low	Low	Low	Low
Ducros et al., 2011[26]	Low	Low	Low	Low	Some concern[f]	Some concern
Callaway et al., 2006[25]	Low	Low	Low	Low	Some concern[f]	Some concern
Silfvast et al., 1985[31]	High[i]	Low	Low	Some concern[c]	Some concern[f]	High
Lindner et al., 1991[32]	Some concern[d]	Low	Low	Some concern[c]	Some concern[f]	Some concern
Callaham et al., 1992[20]	Low	Low	Some concern[l]	Low	Some concern[f]	Some concern

[a] Concern due to missing outcomes data for neurologic outcome only.

[b] Due lack of blinding and differences in cardiopulmonary resuscitation duration (longer in IV drug arm) and number of defibrillations (more in IV drug arm) between groups.

[c] Concern specifically cited when subjective outcomes included (neurologic outcome, manual blood pressure assessment) and assessors not clearly blinded.

[d] Limited information on process.

[e] No information on blinding or other treatment differences between groups.

[f] Unclear whether analysis matched pre-planned protocol (no trial registration or published protocol).

[g] Some baseline imbalance between groups in arrest location, and study drug randomized by code cart placement.

[h] Randomization done by trial statistician and some baseline imbalance between groups.

[i] No information on method and no or minimal baseline characteristics between groups.

[j] No information on analysis method or other treatment differences between groups.

[k] Reported clinical endpoints are different than those in pre-planned protocol.

[l] significant missing data on some arrest response characteristics and not reported how this was distributed between groups.

Epinephrine compared to placebo

Two controlled trials were included for the meta-analyses comparing the use of epinephrine to placebo during OHCA.[8,21] In the pooled analyses for patients with any initial rhythm, the use of epinephrine was associated with increases in ROSC (36% [1521/4247] compared to 12% [490/4222], RR: 3.09 [95% CI: 2.82, 3.39], absolute risk difference: 243 more per 1000 people [95% CI: from 211 to 277 more], high certainty of evidence), survival to hospital admission (24% [1016/4245] compared to 8% [353/4244], RR: 2.88 [95% CI: 2.57, 3.22], absolute risk difference: 156 more per 1000 people [95% CI: from 131 to 185 more], high certainty of evidence), and survival to hospital discharge (3.2% [139/4281] compared to 2.3% [96/4257], RR: 1.44 [95% CI: 1.11, 1.86], absolute risk difference: 10 more per 1000 people [95% CI: from 2 to 19 more], moderate certainty of evidence). There was no significant difference in survival to hospital discharge with a favorable neurological outcome between groups (2.2% [96/4279] compared to 1.9% [79/4256], RR: 1.21 [95% CI: 0.90, 1.62], absolute risk difference: 4 more per 1000 people [95% CI: from 2 fewer to 12 more], moderate certainty of evidence). Additional details are provided in the GRADE table in the Supplemental Content. Forest plots for each analysis are provided in Fig. 2.

Only the more recent, larger trial reported the critical outcomes of 3-month survival and survival with favorable or unfavorable neurologic outcome at 3 months.[8] In that trial, epinephrine increased survival at 3 months (3% [121/4009] compared to 2.2% [86/3991], RR: 1.40 [95% CI: 1.07, 1.84], absolute risk difference: 9 more per 1000 people [95% CI: from 2 to 18 more], moderate certainty of evidence), but did not statistically significantly improve favorable neurologic outcome at 3 months (2.1% [82/3986] compared to 1.6% [63/3979], RR: 1.30 [95% CI: 0.94, 1.80], absolute risk difference: 5 more per 1000 people [95% CI: from 1 fewer to 13 more], low certainty of evidence). The number of survivors with an unfavorable neurologic outcome at 3 months did not differ between groups (0.4% [16/3986] compared to 0.3% [11/3979], RR: 1.45 [95% CI: 0.67, 3.12], absolute risk difference: 1 more per 1000 people [95% CI: from 1 fewer to 6 more], very low certainty of evidence), although the loss to follow up and the very low event rates overall led to very low confidence in this effect estimate.

When separated based on initial rhythm, epinephrine (compared to placebo) was associated with an increase in ROSC for both non-shockable rhythms (33% [1075/ 3282] compared to 7.4% [243/3297], RR: 4.45 [95% CI: 3.91, 5.08], absolute risk difference: 254 more per 1000 people [95% CI: from 214 to 301 more], high certainty of evidence) and shockable rhythms (46% [403/876] compared to 27% [235/865], RR: 1.68 [95% CI: 1.48, 1.92], absolute risk difference: 185 more per 1000 people [95% CI: from 130 to 250 more], moderate certainty of evidence). Epinephrine was also associated with survival to hospital discharge for non-shockable rhythms (1.0% [34/3,302] compared to 0.4% [13/3,317], RR: 2.56 [95% CI: 1.37, 4.80], absolute risk difference: 6 more per 1000 people [95% CI: from 1 to 15 more], moderate certainty of evidence), but not for shockable rhythms (12% [103/883] compared to 9.4% [82/870], RR: 1.23 [0.94, 1.62], absolute risk difference: 22 more per 1000 people [95% CI: from 6 fewer to 58 more], moderate certainty of evidence). Epinephrine appeared to have a more pronounced effect for initial non-shockable rhythms than for initial shockable rhythms (p-value for the interaction between epinephrine and initial rhythm: <0.01 for ROSC and 0.04 for survival to hospital discharge).[101] Additional details are provided in Fig. 3.

In the one trial reporting outcomes by initial rhythm at 3 months, there was no statistically significant difference in survival with favorable neurological outcome at 3 months for those with an initial shockable rhythm (9.2% [69/750] with epinephrine compared to 7.9% [58/732] with placebo, RR: 1.16 [95% CI: 0.83, 1.62], absolute risk difference: 13 more per 1000 people [95% CI: from 13 fewer to 49 more], very low certainty of evidence). For those with an initial non-shockable rhythm, the increase in survival with favorable neurological outcome at 3 months approached statistical significance (0.4% [12/3141] with epinephrine compared to 0.1% [4/3177] with placebo, RR: 3.03 [95% CI: 0.98, 9.38], absolute risk difference: 3 more per 1000 people [95% CI: from 0 fewer to 11 more], low certainty of evidence).[101]

The vast majority of the 46 retrospective cohort studies investigating the effect of administration of epinephrine during cardiac arrest, compared with no administration of epinephrine, found that receiving epinephrine was associated with worse survival and worse neurologic outcome at hospital discharge. However, almost all cohort studies were rated at a critical risk of bias primarily due to uncontrolled confounders and selection bias.[102] Of note, one large observational study that accounted for resuscitation time bias found that epinephrine was associated with improved survival.[65] In contrast, the same dataset was analyzed and published without accounting for resuscitation time bias and concluded that epinephrine was associated with decreased survival.[52] In terms of timing of epinephrine administration, we identified 16 observational studies. Of these, 10 compared the discrete exposures of "early" (variably defined as 1–3 min, <5 min, <10 min, 5–18 min, and 5–20 min) epinephrine compared to "late" epinephrine.[84–93] All of these studies found higher rates of ROSC when epinephrine was administered early, although the critical risk of bias across all studies again limits interpretation of these results. Differences in survival to hospital discharge and favorable neurologic outcome were additionally limited by very low event rates and inconsistent results between studies. Four studies looked at the time to epinephrine as a continuous variable and all of these studies found a slight decrease in odds of ROSC per minute delay in epinephrine administration, with all studies determined to be at critical risk of bias.[96–99]

Vasopressin compared to epinephrine

Three controlled trials were included for the meta-analyses comparing the use of vasopressin to epinephrine during OHCA.[28–30] There was no significant difference between groups in ROSC (27% [212/787] compared to 28% [220/775], RR: 1.05 [95% CI: 0.80, 1.39], absolute risk difference: 14 more per 1000 people [95% CI: from 57 fewer to 111 more], low certainty of evidence), survival to hospital admission (33% [258/787] compared to 29% [225/775], RR: 1.17 [95% CI: 0.82, 1.66], absolute risk difference: 49 more per 1000 people [95% CI: from 52 fewer to 192 more], low certainty of evidence), survival to hospital discharge (9.7% [75/776] compared to 8.7% [67/766], RR: 1.26 [95% CI: 0.76, 2.07], absolute risk difference: 23 more per 1000 people [95% CI: from 21 fewer to 94 more], very low certainty of evidence), or survival to hospital discharge with a favorable neurological outcome (4.3% [32/745] compared to 4.6% [34/734], RR: 0.93 [95% CI: 0.58, 1.49], absolute risk difference: 3 fewer per 1000 people [95% CI: from 19 fewer to

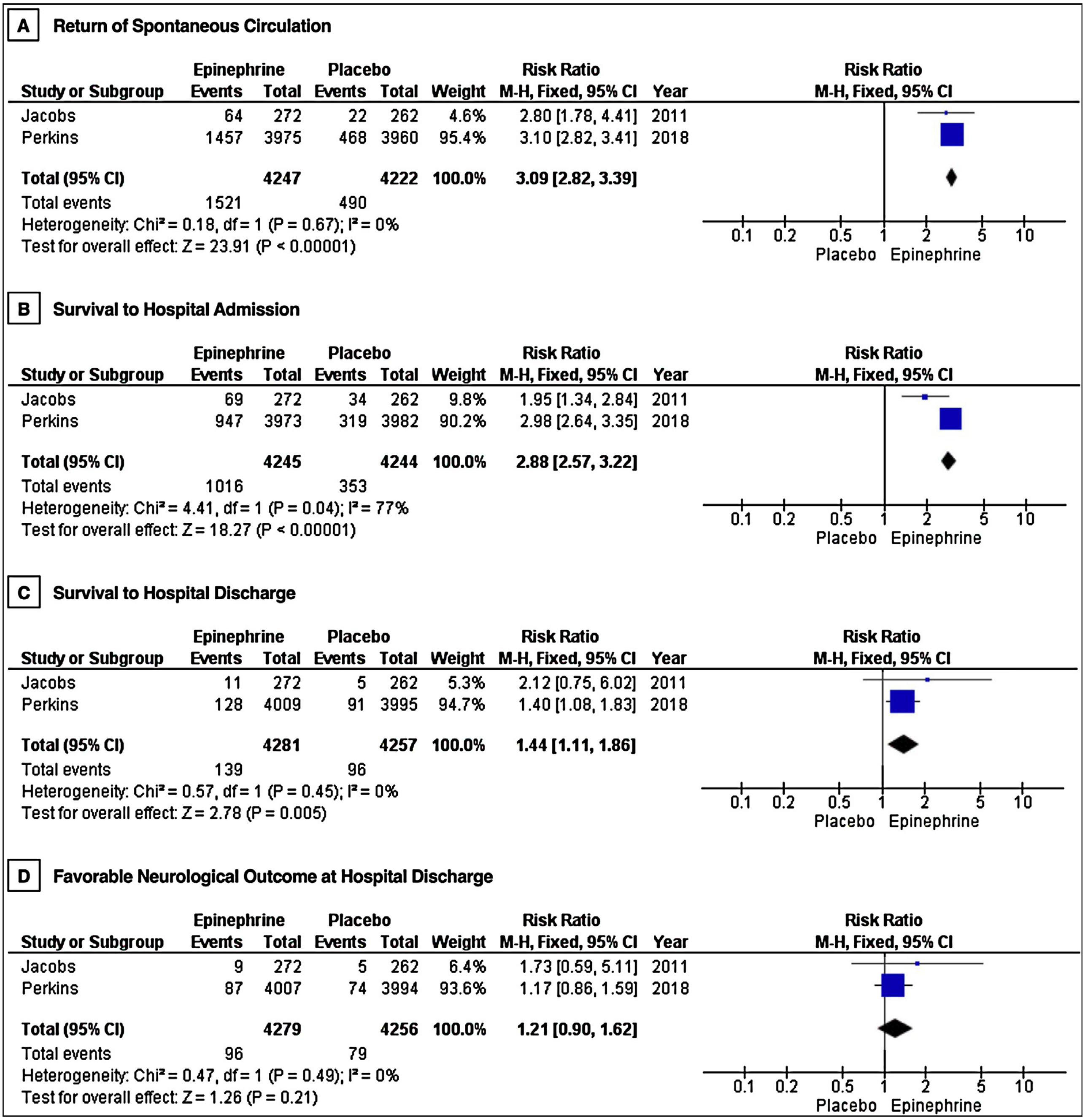

Fig. 2 – Pooled estimates for controlled trials comparing epinephrine to placebo.
Pooled estimates for return of spontaneous circulation (A), survival to hospital admission (B), survival to hospital discharge (C), and favorable neurological outcome at hospital discharge (D). Horizontal lines indicate 95% confidence intervals of the estimate. The studies are ordered by year of publication within each analysis. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel analysis.

23 more], very low certainty of evidence). There was no statistically significant difference when looking at subgroups by initial rhythm (p-value for the interaction between vasopressin and initial rhythm: 0.46 for ROSC and 0.77 for survival to hospital discharge).[101] Forest plots for each analysis are provided in Fig. 4. One additional study of 727 patients that was not pooled due to differences in study design also found no difference in outcomes between groups (very low certainty of evidence for all outcomes).[23]

Initial epinephrine plus vasopressin compared to epinephrine only

Three controlled trials were included for the meta-analyses comparing the use of initial epinephrine plus vasopressin to epinephrine only during OHCA.[25–27] There was no significant difference between groups in ROSC (29% [471/1623] compared to 30% [486/1626], RR: 0.97 [95% CI: 0.87, 1.08], absolute risk

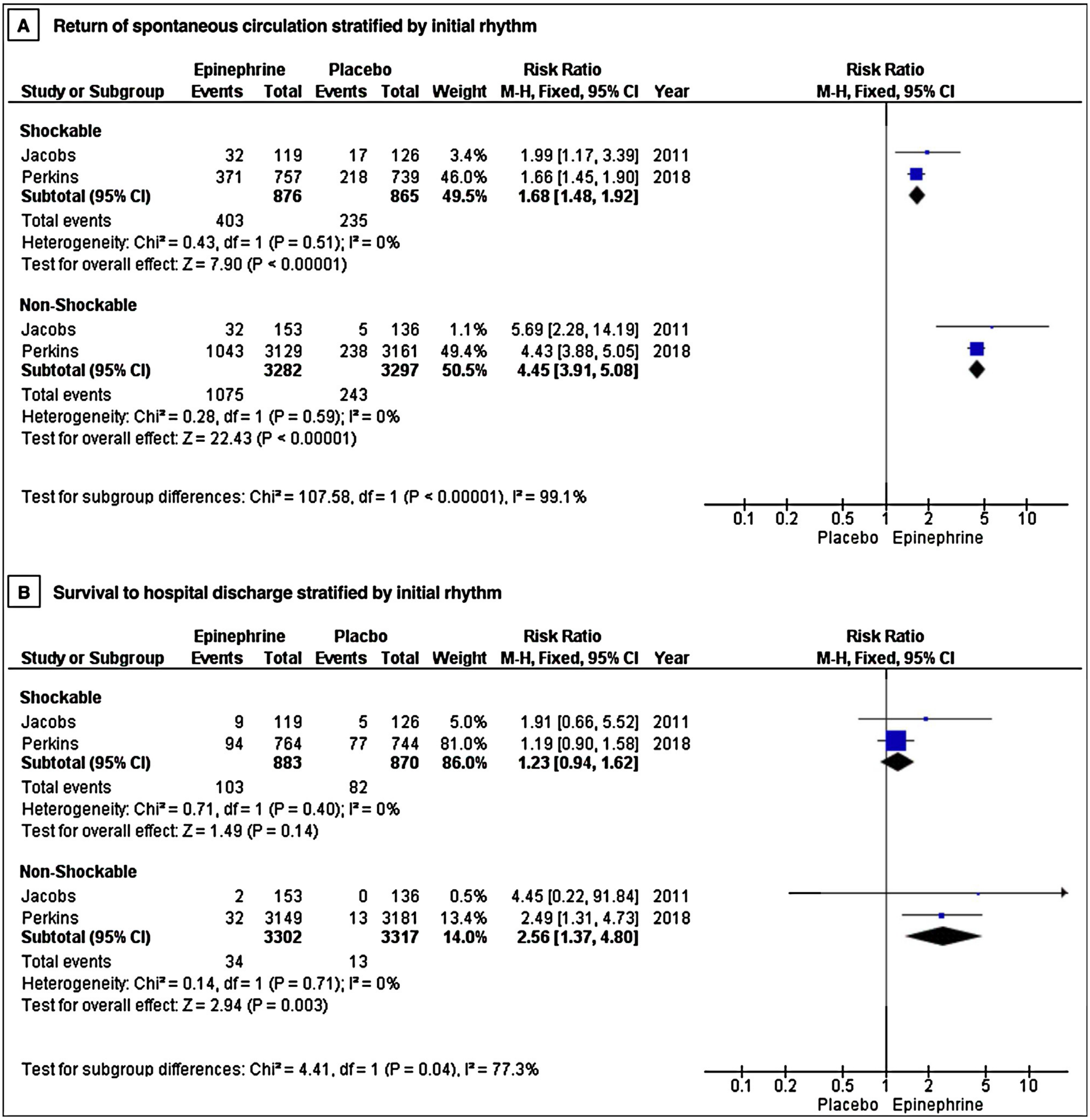

Fig. 3 – Pooled estimates for controlled trials of epinephrine compared to placebo stratified by initial rhythm. Pooled estimates for return of spontaneous circulation (A) and survival to hospital discharge (B) stratified by shockable and non-shockable rhythms. Horizontal lines indicate 95% confidence intervals of the estimate. The studies are ordered by year of publication within each analysis. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel analysis.

difference: 9 fewer per 1000 people [95% CI: from 39 fewer to 24 more], very low certainty of evidence), survival to hospital admission (21% [335/1623] compared to 22% [355/1626], RR: 0.95 [95% CI: 0.83, 1.08], absolute risk difference: 11 fewer per 1000 people [95% CI: from 37 fewer to 17 more], low certainty of evidence), or survival to hospital discharge (1.8% [29/1620] compared to 2.4% [39/1622], RR: 0.76 [95% CI: 0.47, 1.22], absolute risk difference: 6 fewer per 1000 people [95% CI: from 13 fewer to 5 more], very low certainty of evidence). Forest plots for each analysis are provided in Fig. 5.

The observational data on the comparison between vasopressin, vasopressin plus epinephrine, and epinephrine could not be pooled due to heterogeneity and high risk of bias. In the six studies identified, results did not reach statistical significance and were inconsistent between studies.[78–83]

Certainty of evidence across studies

An overview of the overall certainty of evidence across studies is provided in Table 3 and additional information, including GRADE

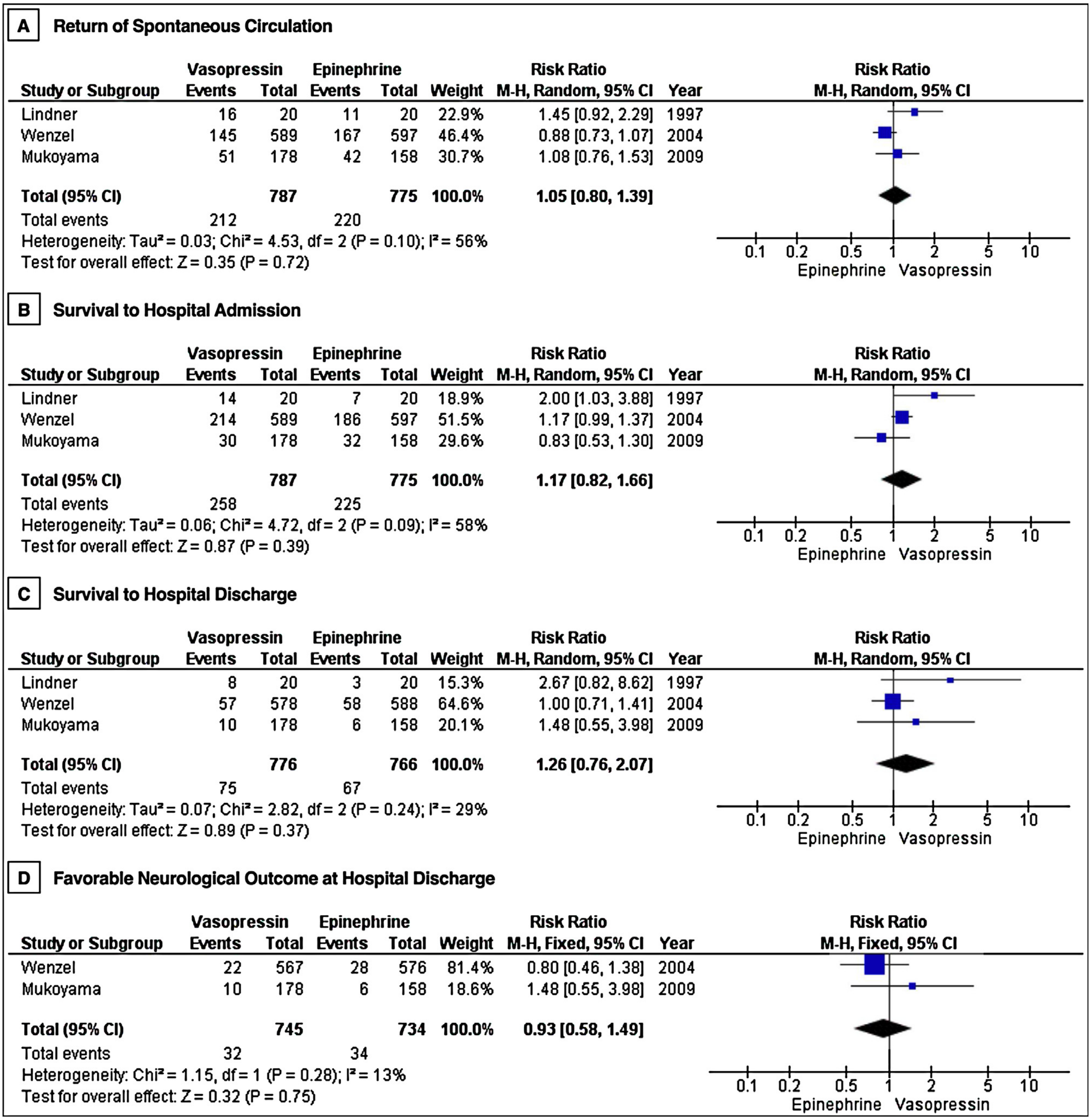

Fig. 4 – Pooled estimates for controlled trials comparing vasopressin to epinephrine.
Pooled estimates for return of spontaneous circulation (A), survival to hospital admission (B), survival to hospital discharge (C), and favorable neurological outcome at hospital discharge (D). Horizontal lines indicate 95% confidence intervals of the estimate. The studies are ordered by year of publication within each analysis. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel analysis.

tables for the comparisons evaluated in controlled trials with footnotes explaining reasons for downgrading, is provided in the Supplemental Content. The certainty of evidence ranged from very low to high for comparisons of epinephrine and placebo, from low to very low for comparisons of vasopressin and epinephrine, and from low to very low for comparisons of initial epinephrine plus vasopressin and epinephrine only.

Discussion

We performed a systematic review with selected meta-analyses evaluating the use of vasopressors in cardiac arrest. The resulting synthesis of existing data and outcomes of the meta-analyses represents a contemporary review of the evidence and will inform the

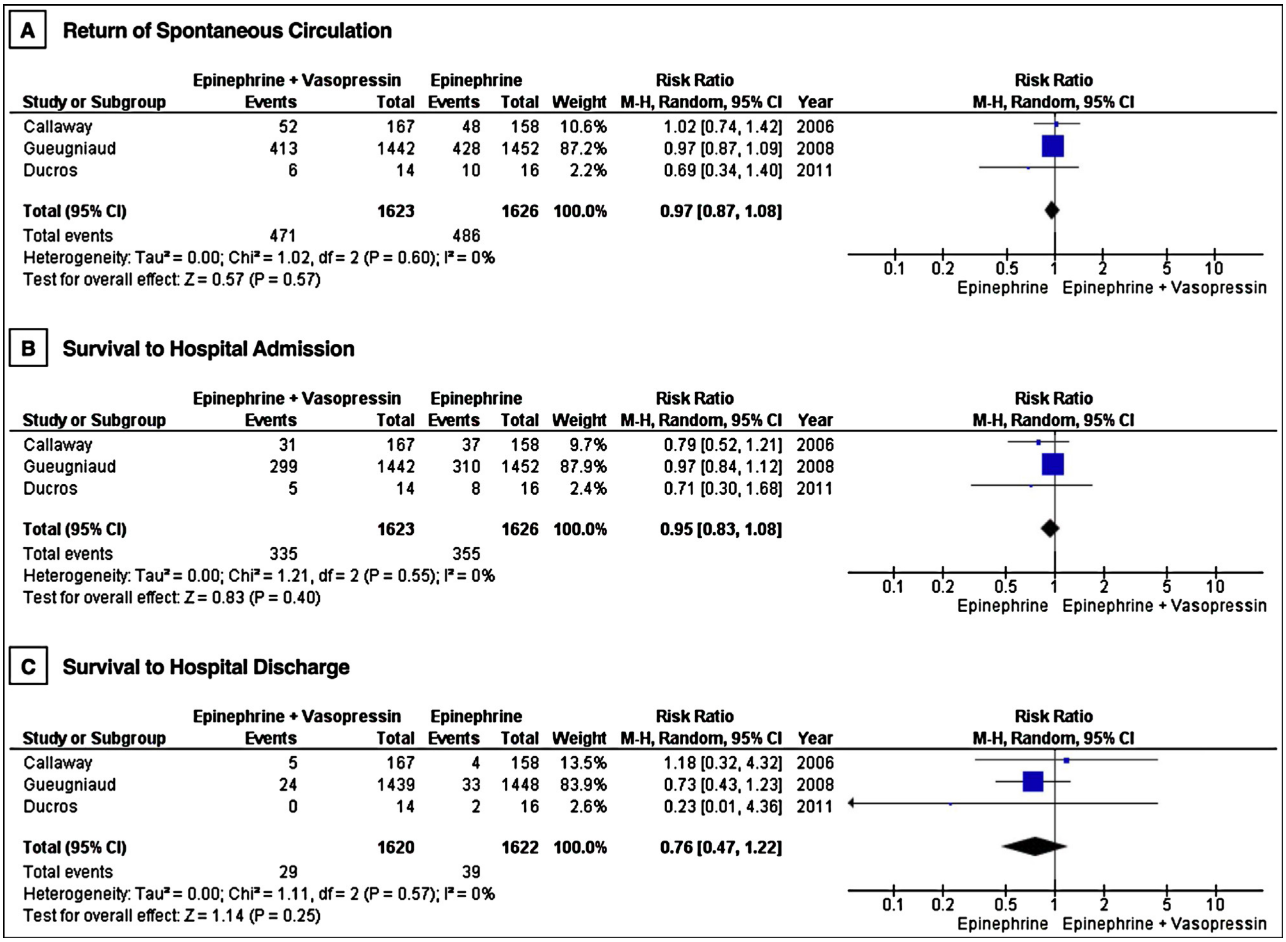

Fig. 5 – Pooled estimates for controlled trials comparing initial epinephrine plus vasopressin to epinephrine only. Pooled estimates for return of spontaneous circulation (A), survival to hospital admission (B), and survival to hospital discharge (C). Horizontal lines indicate 95% confidence intervals of the estimate. The studies are ordered by year of publication within each analysis. Abbreviations: CI, confidence interval.

upcoming ILCOR Consensus on Science and Treatment Recommendation on vasopressor use during cardiac arrest.

For the comparison of epinephrine to placebo, pooled data from randomized trials indicate that epinephrine markedly improves ROSC and survival to hospital admission. Confidence in the findings for these short-term outcomes is high as the data are robust and consistent. For mid-term survival (30-day/hospital discharge), the pooled randomized trial data also indicate overall improved survival in the epinephrine compared to placebo arms, although the confidence in these findings is slightly less robust compared to ROSC and hospital admission. The pooled analysis failed to show improvement in mid-term (hospital discharge) neurological outcome, although this was limited by the low event rate for this outcome, so confidence in this finding was lower.

Although the available data, from a single large trial, has not definitively demonstrated benefit or harm in long-term survival with favorable neurological outcome, whether the results of this trial can be generalized to all cardiac arrest patients remains uncertain. The endpoint of neurological outcome at 3 months in the PARAMEDIC-2 trial was limited by loss to follow up, and perhaps most importantly, the very low number of patients who survived to 3 months in the trial overall. The overall survival rate was extremely low, and at 3 months there were not enough patients alive to provide the statistical power to reliably detect a difference between groups. The difference in the non-shockable rhythm group specifically, with a benefit in neurological outcome approaching significance, raises questions about whether a difference would be detected in a cohort with better overall survival. The authors of the recent trial primarily focused on neurological outcome at hospital discharge, reporting the number of survivors in each group with each level of Modified Rankin Score, noting that more patients in the epinephrine group survived with an unfavorable neurologic outcome compared to the placebo arm at this earlier time point. The Advanced Life Support task force at ILCOR determined *a priori* that when evaluating survival with unfavorable neurologic outcome, only time-points of 3 months or longer after ROSC would be considered. This decision was made based on clinical expertise of the task force, as well as literature suggesting that neurologic recovery after cardiac arrest is often prolonged, and that evaluating this outcome before 3 months may thus be misleading.[103–109]

In pooled randomized data, we found that improvement in both short and long-term outcomes varied depending on the initial rhythm, with a very robust statistically significant increase in ROSC for

Table 3 – Overview of the GRADE approach for selected outcomes.

Study	Setting	Intervention	Comparison	Outcome	Relative risk (95% CI)	Risk difference (95% CI)	Certainty in evidence
Jacobs et al., 2011[21] Perkins et al., 2018[8]	OHCA	Epinephrine	Placebo	Return of spontaneous circulation	3.09 (2.82 to 3.39)	243 more per 1000 (from 211 more to 277 more)	High
Jacobs et al., 2011[21] Perkins et al., 2018[8]	OHCA	Epinephrine	Placebo	Survival to hospital discharge	1.44 (1.11 to 1.86)	10 more per 1000 (from 2 more to 19 more)	Moderate
Jacobs et al., 2011[21] Perkins et al., 2018[8]	OHCA	Epinephrine	Placebo	Favorable neurological outcome at hospital discharge	1.21 (0.90 to 1.62)	4 more per 1000 (from 2 fewer to 12 more)	Moderate
Perkins et al., 2018[8]	OHCA	Epinephrine	Placebo	Survival at 3 months	1.40 (1.07, 1.84)	9 more per 1000 (from 2 more to 18 more)	Moderate
Perkins et al., 2018[8]	OHCA	Epinephrine	Placebo	Favorable neurological outcome at 3 months	1.30 (0.94 to 1.80)	5 more per 1000 (from 1 fewer to 13 more)	Low
Lindner et al., 1997[28] Wenzel et al., 2004[30] Mukoyama et al., 2009[29]	OHCA	Vasopressin	Epinephrine	Return of spontaneous circulation	1.05 (0.80, 1.39)	14 more per 1000 (from 57 fewer to 111 more)	Low
Lindner et al., 1997[28] Wenzel et al., 2004[30] Mukoyama et al., 2009[29]	OHCA	Vasopressin	Epinephrine	Survival to hospital discharge	1.26 (0.76 to 2.07)	23 more per 1000 (from 21 fewer to 94 more)	Very low
Lindner et al., 1997[28] Wenzel et al., 2004[30] Mukoyama et al., 2009[29]	OHCA	Vasopressin	Epinephrine	Favorable neurological outcome at hospital discharge	0.93 (0.58 to 1.49)	3 fewer per 1000 (from 19 fewer to 23 more)	Very low
Ong et al., 2012[23]	OHCA	Vasopressin	Epinephrine	Return of spontaneous circulation	1.06 (0.85 to 1.32)	18 more per 1000 (from 45 fewer to 96 more)	Very low
Ong et al., 2012[23]	OHCA	Vasopressin	Epinephrine	Survival to hospital discharge	1.30 (0.53 to 3.19)	7 more per 1000 (from 11 fewer to 50 more)	Very low
Ong et al., 2012[23]	OHCA	Vasopressin	Epinephrine	Favorable neurological outcome at hospital discharge	0.94 (0.27 to 3.22)	1 fewer per 1000 (from 10 fewer to 31 more)	Very low
Stiell et al., 2001[22]	IHCA	Vasopressin	Epinephrine	Return of spontaneous circulation	1.09 (0.78 to 1.52)	36 more per 1000 (from 87 fewer to 206 more)	Low
Stiell et al., 2001[22]	IHCA	Vasopressin	Epinephrine	Survival to hospital discharge	0.85 (0.41 to 1.77)	20 fewer per 1000 (from 80 fewer to 104 more)	Low
Stiell et al., 2001[22]	IHCA	Vasopressin	Epinephrine	Favorable neurological outcome at hospital discharge	0.71 (0.33 to 1.54)	39 fewer per 1000 (from 91 fewer to 73 more)	Low
Callaway et al., 2006[25] Gueugniaud et al., 2008[27] Ducros et al., 2011[26]	OHCA	Epinephrine plus vasopressin	Epinephrine only	Return of spontaneous circulation	0.97 (0.87 to 1.08)	9 fewer per 1000 (from 39 fewer to 24 more)	Very low
Callaway et al., 2006[25] Gueugniaud et al., 2008[27] Ducros et al., 2011[26]	OHCA	Epinephrine plus vasopressin	Epinephrine only	Survival to hospital discharge	0.76 (0.47 to 1.22)	6 fewer per 1000 (from 13 fewer to 5 more)	Very low
Gueugniaud et al., 2008[27]	OHCA	Epinephrine plus vasopressin	Epinephrine only	Favorable neurological outcome at hospital discharge	0.53 (0.24 to 1.19)	6 fewer per 1000 (from 9 fewer to 2 more)	Low
Olasveengen et al., 2009[33]	OHCA	IV drug	No IV drug	Return of spontaneous circulation	1.60 (1.30 to 1.96)	148 more per 1000 (from 74 more to 237 more)	Very low
Olasveengen et al., 2009[33]	OHCA	IV drug	No IV drug	Survival to hospital discharge	1.13 (0.75 to 1.69)	12 more per 1000 (from 23 fewer to 64 more)	Very low
Olasveengen et al., 2009[33]	OHCA	IV drug	No IV drug	Favorable neurological outcome at hospital discharge	1.21 (0.79 to 1.87)	17 more per 1000 (from 17 fewer to 70 more)	Very low

IV: Intravenous, OHCA: Out-of-hospital cardiac arrest. Several studies allowed for either intravenous or intraosseous administration of study drug, and direct comparison of route of administration was not done.

non-shockable rhythms and a somewhat less pronounced statistically significant improvement in ROSC for shockable rhythms when patients were administered epinephrine compared to placebo (Fig. 3). Survival to hospital discharge was shown to be significantly increased for non-shockable rhythms but not for shockable rhythms, and there was a statistically significant interaction between the epinephrine effect and initial rhythm for both ROSC and survival to hospital discharge. These results suggest that epinephrine, while effective in both circumstances, may be more effective for non-shockable than for shockable rhythms, although the results of subgroup analyses should be interpreted with caution. For example, this analysis was performed based on the initial rhythm and not necessarily the rhythm at the time of the receipt of epinephrine (or placebo). A differential effect of epinephrine for shockable and non-shockable rhythms, if truly present, could be due to the competing definitive therapy of defibrillation for shockable rhythms, as well as the potential role of antiarrhythmics. In contrast, there are limited other therapeutic options for PEA (pulseless electrical activity) and asystole apart from cardiopulmonary resuscitation and potentially treating the underlying cause. Lastly, the timing of administration of epinephrine was inherently different between rhythms with patients with non-shockable rhythms receiving epinephrine as soon as feasible and the protocol for patients with shockable rhythms being to administer epinephrine after the third defibrillation.[110–112]

The timing of epinephrine administration in relation to the onset of cardiac arrest could be an effect modifier, wherein the effectiveness of the vasopressor on important outcomes differs based on the downtime elapsed before the vasopressor is given. Published data regarding the timing of vasopressor administration is limited to observational studies, all of which were found to have a critical risk of bias in this review. Within these limitations, the ten studies comparing “early” to “late” epinephrine uniformly found that earlier epinephrine was associated with better outcomes, particularly for patients with non-shockable rhythms. What is most clear from the available data is that epinephrine increases the chance of ROSC very significantly, especially for those with non-shockable rhythms. The cerebral and other organ ischemia that occur both prior to cardiopulmonary resuscitation start and during cardiopulmonary resuscitation cause the ischemia-reperfusion injury that drives outcome in those who survive the initial arrest. Shorter time-to-ROSC should lessen this injury and is associated with better outcomes. As epinephrine improves the chance of ROSC, it stands to reason that if epinephrine is being given, administering the drug early is likely to be most beneficial. For non-shockable rhythms, the lack of competing interventions and decreased probability of survival with longer duration of cardiopulmonary resuscitation suggests that epinephrine should be administered as soon as feasible. In patients with shockable rhythms, the timing of epinephrine administration with respect to defibrillation is less clear. In both trials in the pooled analysis, for patients with shockable rhythms, the protocol was to administer epinephrine or placebo after the third defibrillation. Whether earlier provision of epinephrine in shockable rhythms would be more beneficial, unchanged, or harmful remains unknown.

Data was pooled from three randomized controlled trials of vasopressin compared to epinephrine as initial vasopressors during out-of-hospital cardiac arrest. In those studies, vasopressin did not lead to improvement in early or mid-term survival or survival with favorable neurologic outcome, compared to epinephrine. Similarly, in the pooled analysis comparing initial epinephrine plus vasopressin to epinephrine alone, there was no significant difference found in any outcome measure. Although the total number of patients in these studies is much less than the total number in the epinephrine vs placebo trials, which limits the certainty of evidence for these comparisons, currently there is no evidence that vasopressin provides benefit over epinephrine. These results join previously reported findings of meta-analyses of randomized trials comparing high-dose epinephrine to standard-dose epinephrine, in which no benefit to high-dose epinephrine was seen.[113] Overall, there is no compelling evidence to suggest an increased benefit when any vasopressor is given in place of, or in addition to, standard-dose epinephrine during resuscitation from cardiac arrest.

The administration of vasopressors has been a major component of cardiac arrest resuscitation for decades, albeit with only limited evidence supporting their effectiveness. As detailed in the present systematic review and meta-analyses, recent randomized trials have substantially expanded the evidence base regarding the use of vasopressors in cardiac arrest and there are now moderate-to-high levels of certainty that epinephrine (as compared to placebo) improves rates of ROSC, survival to hospital admission, and survival to hospital discharge. Despite the recent large trial, however, the data on longer term survival and neurologic outcome remain inconclusive, in large part due to the challenges of obtaining large enough sample sizes to detect differences in such low-frequency outcomes, as well as loss to follow up for longer-term neurologic outcomes.

Several unanswered questions remain regarding the relationship between the time from cardiac arrest to vasopressor administration and outcomes in non-shockable rhythms and the timing of vasopressor administration with respect to defibrillation in patients with shockable rhythms, and these questions should be addressed in future studies. Additionally, the route of administration, quality of cardiopulmonary resuscitation, and post-resuscitation care were not addressed in the current review and it remains unclear whether these and other characteristics could modify the effect of vasopressors. For example, neither Perkins et al.[8] nor Jacobs et al.[21] accounted for post-resuscitation care, and the number of subjects receiving targeted temperature management or other therapies remains unknown. Differences in post-resuscitation care between health care systems could theoretically impact the number of subjects achieving ROSC who survive with favorable (or unfavorable) neurological outcome. The very poor survival in these two trials, as mentioned above, also may or may not be generalizable to other health care systems. Finally, data on IHCA remains extremely limited. The differences between IHCA and OHCA are many, including patient characteristics and significantly shorter times to drug administration during cardiopulmonary resuscitation.[114] How epinephrine impacts outcome after IHCA could therefore be significantly different than what has been seen in OHCA and should be explored further.

Conclusion

Randomized controlled trial data indicate that epinephrine improves ROSC, survival to hospital discharge, and 3-month survival in OHCA. The improvement in ROSC and survival to hospital discharge from epinephrine appeared more pronounced in patients with non-shockable rhythms compared to shockable rhythms. Differences in long-term neurological outcome did not reach statistical significance, although there was a signal toward improved outcomes. Randomized controlled trial data indicated no benefit from vasopressin compared to epinephrine or vasopressin combined with epinephrine compared to epinephrine only.

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Conflicts of interest

Dr. Lars W. Andersen (author) is the Principal Investigator of a randomized trial evaluating the combination of epinephrine/steroids versus placebo for in-hospital cardiac arrest, and Dr. Donnino (author) is a non-paid consultant on that trial (NCT03640949). Trials including epinephrine/steroids were excluded from this review prior to commission. Drs. Donnino, Berg, Andersen, (authors) and Callaway (collaborator) have published observational studies that were included in this review. Dr. Jerry Nolan (collaborator) is co-author on a randomized trial evaluating epinephrine versus placebo that was included in this review Dr. Nolan was not directly involved as an investigator in this systematic review however he did review the findings and participate in Task Force discussions on synthesis of the data as a Task Force member.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.04.008.

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