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Epinephrine in Out-of-Hospital Cardiac Arrest

A Network Meta-analysis and Subgroup Analyses of Shockable and Nonshockable Rhythms

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BACKGROUND: Epinephrine is the most commonly used drug in out-of-hospital cardiac arrest (OHCA) resuscitation, but evidence supporting its efficacy is mixed.

RESEARCH QUESTION: What are the comparative efficacy and safety of standard dose epinephrine, high-dose epinephrine, epinephrine plus vasopressin, and placebo or no treatment in improving outcomes after OHCA?

STUDY DESIGN AND METHODS: In this systematic review and network meta-analysis of randomized controlled trials, we searched six databases from inception through June 2022 for randomized controlled trials evaluating epinephrine use during OHCA resuscitation. We performed frequentist random-effects network meta-analysis and present ORs and 95% CIs. We used the the Grading of Recommendations, Assessment, Development, and Evaluation approach to rate the certainty of evidence. Outcomes included return of spontaneous circulation (ROSC), survival to hospital admission, survival to discharge, and survival with good functional outcome.

RESULTS: We included 18 trials (21,594 patients). Compared with placebo or no treatment, high-dose epinephrine (OR, 4.27; 95% CI, 3.68-4.97), standard-dose epinephrine (OR, 3.69; 95% CI, 3.32-4.10), and epinephrine plus vasopressin (OR, 3.54; 95% CI, 2.94-4.26) all increased ROSC. High-dose epinephrine (OR, 3.53; 95% CI, 2.97-4.20), standard-dose epinephrine (OR, 3.00; 95% CI, 2.66-3.38), and epinephrine plus vasopressin (OR, 2.79; 95% CI, 2.27-3.44) all increased survival to hospital admission as compared with placebo or no treatment. However, none of these agents may increase survival to discharge or survival with good functional outcome as compared with placebo or no treatment. Compared with placebo or no treatment, standard-dose epinephrine improved survival to discharge among patients with nonshockable rhythm (OR, 2.10; 95% CI, 1.21-3.63), but not those with shockable rhythm (OR, 0.85; 95% CI, 0.39-1.85).

INTERPRETATION: Use of standard-dose epinephrine, high-dose epinephrine, and epinephrine plus vasopressin increases ROSC and survival to hospital admission, but may not improve survival to discharge or functional outcome. Standard-dose epinephrine improved survival to discharge among patients with nonshockable rhythm, but not those with shockable rhythm.

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KEY WORDS: critical care medicine; emergency medicine; epinephrine; out-of-hospital cardiac arrest; return of spontaneous circulation

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Take-home Points

Study Question: What are the comparative efficacy and safety of standard-dose epinephrine, high-dose epinephrine, epinephrine plus vasopressin, and placebo or no treatment in improving outcomes after out-of-hospital cardiac arrest?

Results: In this network meta-analysis of 18 randomized trials (21,594 patients), standard-dose epinephrine, high-dose epinephrine, and epinephrine plus vasopressin all improved return of spontaneous circulation (ROSC) and survival to hospital admission, but not survival to discharge or functional outcome, as compared with placebo or no treatment. Standard-dose epinephrine improved survival to discharge in nonshockable arrest, but not shockable arrest.

Interpretation: Use of standard-dose epinephrine, high-dose epinephrine, and epinephrine plus vasopressin increases ROSC and survival to hospital admission, but may not improve survival to discharge or functional outcome. Standard-dose epinephrine improved survival to discharge among patients with nonshockable rhythm, but not those with shockable rhythm.

Out-of-hospital cardiac arrest (OHCA) remains an important cause of morbidity and mortality worldwide. Incidence rates of OHCA vary between 30 and 60 per 100,000 person-years, and only 11% to 30% of patients experiencing OHCA survive to hospital discharge.[1] Current advanced life support guidelines recommend the use of one or more doses of 1-mg epinephrine (adrenaline) during adult CPR to increase the chance of return of spontaneous circulation (ROSC).[2-4] The physiologic rationale for epinephrine use during OHCA comes from its effects in stimulating α-receptors in the peripheral vasculature, increasing systemic vascular resistance, aortic diastolic pressure, and cardiac contractility.[5,6] This physiologic rationale was supported by early nonhuman studies,[7] and use of epinephrine is common in OHCA treatment worldwide.[8]

Despite the widespread use of epinephrine in OHCA, high-certainty data supporting its efficacy in improving patient-centered outcomes are limited.[9] Although some observational data have suggested improved survival to hospital discharge after OHCA,[10,11] other registries have found that epinephrine use is associated with increased ROSC, but not survival with good functional outcome, and may be associated with worse patient-centered outcomes.[12] As such, evaluation of randomized evidence surrounding the use of epinephrine is a priority, particularly in relationship to dose response and comparison with placebo. Previous traditional meta-analyses have shown that epinephrine improves overall survival in OHCA, but these reviews have been limited to direct comparison of the few trials comparing epinephrine with placebo.[13-16] To overcome this, we conducted a systematic review and network meta-analysis of randomized controlled trials (RCTs), allowing us to harness the cumulative data from all trials

ABBREVIATIONS: GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; OHCA = out-of-hospital cardiac arrest; RCT = randomized controlled trial; ROSC = return of spontaneous circulation; SUCRA = surface under the cumulative ranking curve

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in a particular condition and to generate indirect estimates of the effect between treatments that have not been compared previously. The purpose was to evaluate the relative efficacy and safety of four pharmacologic treatments in adult patients with OHCA: standard-dose epinephrine (1 mg or 0.01-0.02 mg/kg), high-dose epinephrine (single dose of ≥ 5mg or ≥ 0.1 mg/kg), the combination of standard-dose epinephrine and vasopressin, and vasopressin alone (without epinephrine), as compared with each other and with placebo or no treatment. We hypothesized that standard-dose epinephrine would be superior to other agents in improving survival and functional outcome. We secondarily conducted separate network meta-analyses among patients with shockable OHCA and those with nonshockable OHCA. We hypothesized that epinephrine would be beneficial in nonshockable OHCA, but not in shockable OHCA.

Study Design and Methods

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement extension for network meta-analysis,[17,18] and registered our protocol with the Center for Open Science.

Data Sources and Search Strategy

We searched six databases (Medline, PubMed, Embase, Scopus, Web of Science, and the Cochrane Database of Systematic Reviews) from inception through June 24, 2022. In consultation with the review authors, an experienced health sciences librarian developed the search strategy (e-Fig 1). We conducted further surveillance searches using the related articles feature[19] and performed an extensive search of the unpublished literature, including the reference lists of all included studies and existing traditional systematic reviews of epinephrine in OHCA.[13,15,16]

Study Selection

Two reviewers independently screened titles and abstracts using Covidence software. These same reviewers independently assessed full texts of potentially eligible trials for inclusion. Disagreements were resolved through discussion and consensus. We included published full-text RCTs (parallel, cluster, or cross-over), without language restriction, meeting the following criteria: (1) enrolled adult patients (≥ 16 years of age), (2) conducted in patients with nontraumatic OHCA (with any initial cardiac rhythm and regardless of presumed underlying cause), (3) randomized patients to a treatment arm that protocolized the use of epinephrine (eg, either standard-dose epinephrine, high-dose epinephrine, the combination of epinephrine and vasopressin, vasopressin alone [without epinephrine], or placebo or no intravascular drug treatment), and (4) reported at least one of the outcomes of interest (described herein). We excluded: (1) trials that exclusively used nonintravascular routes for epinephrine administration (eg, via tracheal tube, intraosseous, or IM), (2) secondary analyses that evaluated subgroups of patients enrolled in larger RCTs, and (3) trials that used a nonrandomized control cohort. In RCTs enrolling patients with both OHCA and in-hospital cardiac arrest (IHCA), we evaluated only patients with OHCA. When data for patients with OHCA was not presented separately, we contacted authors to obtain primary data only from patients with OHCA.

We evaluated multiple outcomes on the basis of the Utstein reporting framework (which includes patient and public involvement),[20] including ROSC at any time point, survival to hospital admission, survival to hospital discharge (or the latest time point reported up until 6 months after discharge), and survival with good functional outcome at discharge (or the latest time point reported until 6 months after discharge). Good functional outcome was defined on the basis of any of the following: (1) modified Rankin scale score of 0 (no symptoms at all) to 3 (moderate disability), (2) Cerebral Performance Categories scale score of 1 (good cerebral performance) or 2 (moderate cerebral disability), or (3) assessment from a health professional indicating no, mild, or moderate disability.

Data Extraction

One investigator used a predesigned data extraction form to collect the following variables: author information, publication year, eligibility criteria, and number of patients (e-Table 1). Two investigators independently collected data related to descriptions of interventions and outcomes. Disagreements were resolved through discussion and consensus.

Risk of Bias Assessment

Two reviewers independently assessed risk of bias of the included studies, using the RoB 2 Cochrane Collaboration tool.[21] We assessed each included trial as having high, low, or possible ("some concerns") risk of bias in each of the five domains of the RoB 2 tool: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results. Disagreements were resolved through discussion and consensus.

Data Synthesis and Analysis

We calculated ORs and corresponding 95% CIs. Initially, we performed conventional pairwise meta-analysis using a DerSimonian and Laird random-effects model for all comparisons with two RCTs or more.[22] We assessed heterogeneity between RCTs for each direct comparison using visual inspection of forest plots, the I^2 statistic, and Cochran's Q statistic. We evaluated the feasibility of conducting network meta-analysis by evaluating: (1) the availability of evidence (eg, number of trials, number of interventions); (2) the homogeneity of study designs, patients, and characteristics of interventions across the body of evidence (transitivity assumption); (3) the structural properties of the network of evidence (eg, connectivity); and (4) coherence in the network and in each closed loop of evidence.

We performed frequentist random-effects network meta-analysis using multivariate meta-analysis assuming a common heterogeneity parameter.[23,24] We assessed global incoherence of the network using the design-by-treatment interaction model (global test), as described by Higgins et al.[25] We used the node-splitting method to assess for incoherence between direct and indirect estimates.[26,27] For each outcome, we estimated ranking probabilities using the surface under the cumulative ranking curve (SUCRA) and generated mean treatment rankings. For all direct comparisons, we assessed small study effects using Harbord's test when ≥ 10 RCTs were available.[28] In sparse networks, using a random-effects model with a common heterogeneity assumption for network meta-analysis can lead to CIs of the network estimates that are wider than those of the direct estimate or the indirect estimate, even when direct and indirect estimates are coherent, leading to spurious imprecision.[29] In such

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instances, we used a fixed-effect model as our primary analysis and presented results from the random-effects model as a sensitivity analysis. We conducted all analyses using STATA version 16 software (StataCorp).

Subgroup Analyses

Initial rhythm has important prognostic associations with outcomes after OHCA.[30] Therefore, where available, we separately extracted data from included trials for patients with initial shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia) and those with initial nonshockable rhythm (pulseless electrical activity or asystole). We then conducted separate network meta-analyses among these subgroups. We hypothesized that epinephrine would be beneficial in nonshockable OHCA, but not shockable OHCA. Finally, we performed network meta-regression to assess for effect modification by risk of bias.

Assessment of Certainty of Evidence

We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to assess the certainty of evidence for each network estimate.[31] To rate the certainty of network estimates, both direct and indirect comparisons are considered. Initially, we rated the certainty in direct estimates according to traditional GRADE guidance, considering risk of bias, imprecision, inconsistency, indirectness, and publication bias.[31] We then rated the certainty in the indirect estimate, with a focus on the most dominant first-order loop. Imprecision for each comparison was assessed at the network level, and not at the level of the direct or indirect estimate. We used a minimally contextualized approach to evaluate certainty in outcomes.[32] As recommended by GRADE guidance, we applied informative narrative statements ("probably," "possibly," "may") to communicate our confidence in the effect estimates.[33]

Results

Search Results, Study Characteristics, and Risk of Bias

We identified 13,884 citations (Fig 1) and screened 10,922 after removal of duplicates. Of these, 33 underwent full-text review. In total, we included 18 RCTs,[34-51] with a combined total of 21,594 patients. One of these publications[45] was a secondary analysis of the original RCT.[52] One trial enrolled both patients with OHCA and patients with IHCA,[50] but we included only patients with OHCA in the meta-analysis. Characteristics of the included trials are shown in e-Tables 2 and 3. Risk-of-bias assessments are shown in e-Table 4. Seven of the included trials were deemed to have at least some risk of bias,[34,35,37,39,44,45] whereas the remaining trials were deemed to be low risk in all domains. Drug allocation was double-blinded in all trials, with the exception of three trials.[44,45,48] Some concerns were noted regarding allocation concealment in three trials[34,39,44] and allocation sequencing in three trials.[35,39,44] Contribution matrices are shown in e-Figure 2.

Return of Spontaneous Circulation

A summary of findings, including network estimates, for ROSC is shown in Table 1. Network diagram, SUCRA table, and estimates of incoherence are shown in e-Table 5. Compared with placebo or no treatment, high-dose epinephrine (OR, 4.27; 95% CI, 3.68-4.97), standard-dose epinephrine (OR, 3.69; 95% CI, 3.32-4.10), epinephrine plus vasopressin (OR, 3.54; 95% CI, 2.94-4.26), and vasopressin alone (OR, 3.53; 95% CI, 2.82-4.41) all increased the incidence of ROSC (all high certainty). Compared with standard-dose epinephrine, high-dose epinephrine probably increased the incidence of ROSC (OR, 1.16; 95% CI, 1.04-1.29; moderate certainty), whereas epinephrine plus vasopressin probably had no effect on ROSC (OR, 0.96; 95% CI, 0.83-1.12; moderate certainty).

Survival to Hospital Admission

The efficacy of the evaluated agents for survival to hospital admission is depicted in Table 2. The network diagram, SUCRA table, and incoherence estimates are displayed in e-Table 6. As compared with placebo or no treatment, vasopressin alone (OR, 4.11; 95% CI, 3.01-5.60), high-dose epinephrine (OR, 3.53; 95% CI, 2.97-4.20), standard-dose epinephrine (OR, 3.00; 95% CI, 2.66-3.38), and epinephrine plus vasopressin (OR, 2.79; 95% CI, 2.27-3.44) all increased survival to hospital admission after OHCA (all high certainty). High-dose epinephrine probably increased survival to hospital admission compared with standard-dose epinephrine (OR, 1.18; 95% CI, 1.04-1.34; moderate certainty). No important differences in survival to hospital admission were likely between epinephrine plus vasopressin and standard-dose epinephrine (OR, 0.93; 95% CI, 0.79-1.10; moderate certainty).

Survival to Hospital Discharge

The network estimates for survival to hospital discharge are displayed in Table 3. The network diagram, SUCRA table, and incoherence estimates are included in e-Table 7. GRADE certainty was limited because of imprecision and low incidence of the outcome. Compared with placebo or no treatment, no important difference in survival to hospital discharge may have existed with standard-dose epinephrine (OR, 1.14; 95% CI, 0.90-1.44; low certainty). Uncertain effect of high-dose epinephrine (OR, 1.10; 95% CI, 0.76-1.60), epinephrine plus vasopressin (OR, 1.06; 95% CI, 0.66-1.71), and vasopressin alone (OR, 1.35; 95% CI, 0.88-2.06) was found in improving survival to hospital

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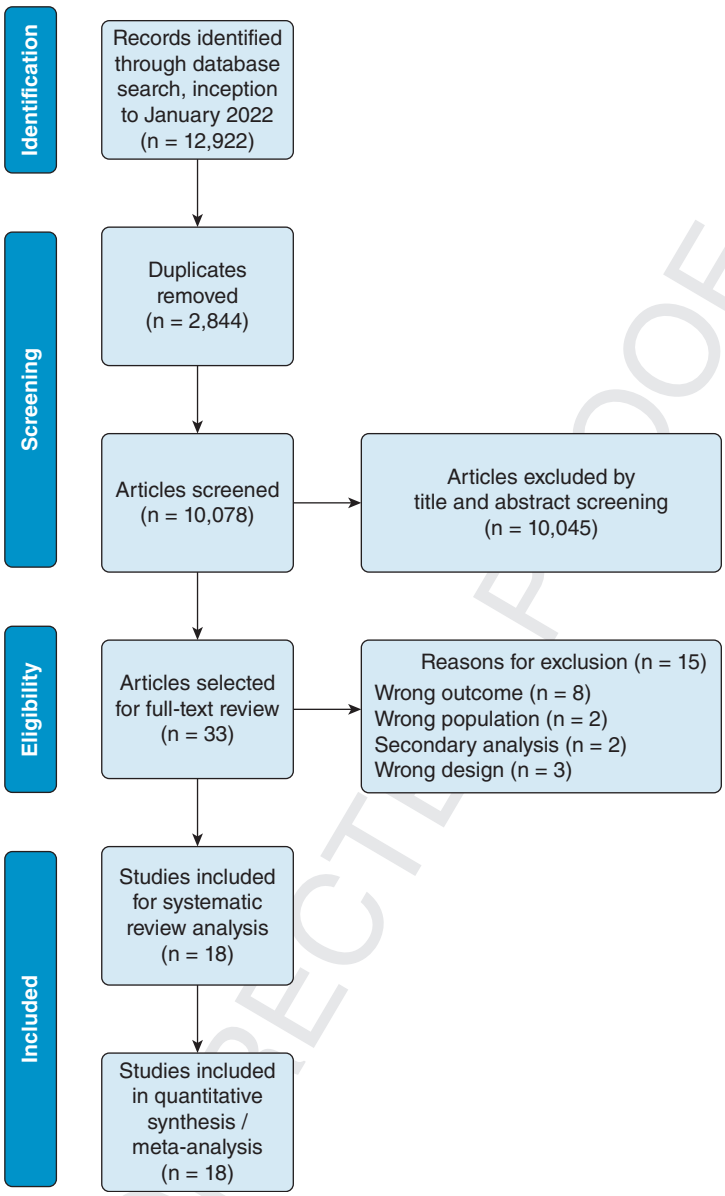

Figure 1 – *Flow chart summarizing evidence search and study selection.*

discharge compared with placebo or no treatment (very low certainty).

Survival with Good Functional Outcome

Network estimates describing the efficacy of these therapies in improving survival with good functional outcome are displayed in Table 4. The network diagram, SUCRA table, and incoherence estimates are shown in e-Table 8. GRADE certainty was limited because of imprecision and low incidence of the outcome. Compared with placebo or no treatment, we found that standard-dose epinephrine may have had no effect on survival with good functional outcome (OR, 0.95; 95% CI, 0.73-1.24; low certainty). The effect of high-dose epinephrine (OR, 0.91; 95% CI, 0.58-1.41) and vasopressin (OR, 0.99; 95% CI, 0.51-1.91) on improving survival with good functional outcome compared with placebo or no treatment was uncertain (very low certainty). Finally, high-dose epinephrine may have had no effect on survival with good functional outcome compared with standard-dose epinephrine (OR, 0.96; 95% CI, 0.67-1.36; low certainty).

Subgroup Analyses: Shockable vs Nonshockable Initial Rhythm

We separately compared patients with nonshockable rhythms and those with shockable rhythms, as extracted from the included trials (Table 5). Network plots and

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TABLE 1] Network Estimates Evaluating the Efficacy of Pharmacologic Agents for ROSC After Out-of-Hospital Cardiac Arrest

Intervention 1	Intervention 2	Network Estimate[a]	GRADE	Narrative Summary
Epinephrine (standard dose)	Placebo or no treatment	3.69 (3.32-4.10)	High	Standard-dose epinephrine increases ROSC compared with no treatment
Epinephrine (high dose)	Placebo or no treatment	4.27 (3.68-4.97)	High[b]	High-dose epinephrine increases ROSC compared with no treatment
Epinephrine plus vasopressin	Placebo or no treatment	3.54 (2.94-4.26)	High	Epinephrine plus vasopressin increases ROSC compared with no treatment
Vasopressin	Placebo or no treatment	3.53 (2.82-4.41)	High	Vasopressin increases ROSC compared with no treatment
Epinephrine (high dose)	Epinephrine (standard dose)	1.16 (1.04-1.29)	Moderate[c]	High-dose epinephrine probably increases ROSC compared with standard-dose epinephrine
Epinephrine (high dose)	Epinephrine plus vasopressin	1.21 (1.00-1.45)	Low[c,d]	High-dose epinephrine may increase ROSC compared with epinephrine plus vasopressin
Epinephrine (high dose)	Vasopressin	1.21 (0.97-1.52)	Low[c,d]	High-dose epinephrine may increase ROSC compared with vasopressin
Epinephrine (standard dose)	Vasopressin	1.05 (0.86-1.27)	Low[e]	Standard-dose epinephrine may have no effect on ROSC compared with vasopressin
Epinephrine plus vasopressin	Epinephrine (standard dose)	0.96 (0.83-1.12)	Moderate[d]	Epinephrine plus vasopressin probably has no effect on ROSC compared with standard-dose epinephrine
Epinephrine plus vasopressin	Vasopressin	1.00 (0.78-1.29)	Low[e]	Epinephrine plus vasopressin may have no effect on ROSC compared with vasopressin

Data are presented as OR (95% CI). GRADE = Grading of Recommendations Assessment, Development, and Evaluation; ROSC = return of spontaneous circulation.

[a]Imprecision incorporated only at network level, not at direct or indirect.

[b]Lowered for risk of bias in included trials, but certainty increased back to high for magnitude of effect.

[c]Lowered for risk of bias in included trials.

[d]Lowered for imprecision.

[e]Lowered two levels for imprecision because CI does not exclude benefit or harm.

SUCRA tables are shown in e-Tables 9-14. Among patients with initial nonshockable rhythms, standard-dose epinephrine increased ROSC (OR, 6.06; 95% CI, 4.71-7.79), survival to hospital admission (OR, 3.94; 95% CI, 2.61-5.95), and survival to discharge (OR, 2.10; 95% CI, 1.21-3.63). However, among patients with initial shockable rhythms, standard-dose epinephrine increased ROSC (OR, 1.87; 95% CI, 1.20-2.45), but not survival to hospital admission (OR, 1.35; 95% CI, 0.73-2.52) or survival to discharge (OR, 0.85; 95% CI, 0.39-1.85). Data were insufficient in the individual subgroups to perform network meta-analyses investigating survival with good functional outcome. Network meta-regression did not show effect modification by risk of bias (e-Fig 3).

Discussion

The use of epinephrine is common during OHCA resuscitation and currently is recommended by clinical practice guidelines from the American Heart Association and the European Resuscitation Council, based on the consensus on science and treatment recommendations of the International Liaison Committee on Resuscitation.[2-4] However, evidence on its efficacy is mixed. Traditional meta-analyses largely have shown potential benefit of standard-dose epinephrine over placebo in improving survival, but without improvement in functional outcomes.[13-16] This controversy was fueled further by the PARAMEDIC-2 trial,[47] which found that standard-dose epinephrine improved 30-day survival, but no statistically significant improvement was seen in the secondary outcomes of survival with good functional outcome. Only one previous network meta-analysis has been conducted addressing this question,[53] but this review did not include PARAMEDIC-2, and mixed trials of IHCA and OHCA, erroneously concluding that the combination of vasopressin, corticosteroids, and epinephrine is the most

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TABLE 2] Network Estimates Evaluating the Efficacy of Pharmacologic Agents for Survival to Hospital Admission After Out-of-Hospital Cardiac Arrest

Intervention 1	Intervention 2	Network Estimate[a]	GRADE	Narrative Summary
Epinephrine (standard dose)	Placebo or no treatment	3.00 (2.66-3.38)	High	Standard-dose epinephrine increases survival to hospital admission compared with no treatment
Epinephrine (high dose)	Placebo or no treatment	3.53 (2.97-4.20)	High[b]	High-dose epinephrine increases survival to hospital admission compared with no treatment
Epinephrine plus vasopressin	Placebo or no treatment	2.79 (2.27-3.44)	High	Epinephrine plus vasopressin increases survival to hospital admission compared with no treatment
Vasopressin	Placebo or no treatment	4.11 (3.01-5.60)	High	Vasopressin increases survival to hospital admission compared with no treatment
Epinephrine (high dose)	Epinephrine (standard dose)	1.18 (1.04-1.34)	Moderate[c]	High-dose epinephrine probably increases survival to hospital admission compared with standard-dose epinephrine
Epinephrine (high dose)	Epinephrine plus vasopressin	1.26 (1.03-1.56)	Low[c,d]	High-dose epinephrine may increase survival to hospital admission compared with epinephrine plus vasopressin
Epinephrine (high dose)	Vasopressin	0.86 (0.63-1.18)	Very Low[b,e]	Effect of high-dose epinephrine compared with vasopressin on survival to hospital admission is uncertain
Epinephrine (standard dose)	Vasopressin	0.73 (0.55-0.97)	Moderate[d]	Vasopressin may increase survival to hospital admission compared with standard-dose epinephrine
Epinephrine plus vasopressin	Epinephrine (standard dose)	0.93 (0.79-1.10)	Low[e]	No difference may exist between epinephrine plus vasopressin compared with standard-dose epinephrine on survival to hospital admission
Epinephrine plus vasopressin	Vasopressin	0.68 (0.49-0.95)	Moderate[d]	Epinephrine plus vasopressin may increase survival to hospital admission compared with vasopressin

Data are presented as OR (95% CI). GRADE = Grading of Recommendations Assessment, Development, and Evaluation.
[a]Imprecision incorporated only at network level, not at direct or indirect.
[b]Lowered for risk of bias in included trials, but certainty increased back to high for magnitude of effect.
[c]Lowered for risk of bias in included trials.
[d]Lowered for imprecision.
[e]Lowered two levels for imprecision because CI does not exclude benefit or harm.

effective in improving survival, a treatment that has been used only in the IHCA population and since has been shown to improve rate of ROSC, but not survival or neurologic outcomes.[54,55]

In this regard, our review is novel and addresses an important question. Not only have we included all the randomized data comparing standard-dose epinephrine with placebo or no treatment, but the network meta-analysis design allowed us to leverage additional trials and to compare additional treatments that have not been tested against placebo or no treatment or each other in an RCT. Our results mostly are consistent with those of the PARAMEDIC-2 trial. Although achieving ROSC and survival to hospital admission may be valuable in facilitating further interventions (such as coronary revascularization), the absence of benefit in patient-oriented outcomes (survival and functional outcome) shown in our review casts doubt on the routine use of these agents in OHCA resuscitation. Of note, given inherent differences in epidemiologic features and outcomes, we deliberately included only patients with OHCA, and therefore it is unknown whether these conclusions apply to patients with IHCA.

The question of whether the potential beneficial cardiovascular effects of epinephrine are outweighed by theoretical cerebrovascular harms is controversial.[9] Some experimental evidence shows that epinephrine may cause harm by worsening brain tissue perfusion, suggesting that the short-term benefits of increased ROSC and survival to hospital admission may be offset by impact on longer-term outcomes.[56] However, other studies using animal models have shown that epinephrine improves cerebral oxygenation and metabolism.[57,58] Most likely, epinephrine does increase

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TABLE 3] Network Estimates Evaluating the Efficacy of Pharmacologic Agents for Survival to Discharge After Out-of-Hospital Cardiac Arrest

Intervention 1	Intervention 2	Network Estimate[a]	GRADE	Narrative Summary
Epinephrine (standard dose)	Placebo or no treatment	1.14 (0.90-1.44)	Low[b,c]	No difference in survival may exist between standard-dose epinephrine and no treatment
Epinephrine (high dose)	Placebo or no treatment	1.10 (0.76-1.60)	Very low[b,c,d]	The effect of high-dose epinephrine compared with no treatment on survival is uncertain
Epinephrine plus vasopressin	Placebo or no treatment	1.06 (0.66-1.71)	Very low[b,e]	The effect of epinephrine plus vasopressin compared with no treatment on survival is uncertain
Vasopressin	Placebo or no treatment	1.35 (0.88-2.06)	Very low[b,e]	The effect of vasopressin compared with no treatment on survival is uncertain
Epinephrine (high dose)	Epinephrine (standard dose)	0.96 (0.72-1.29)	Very low[d,e]	The effect of high-dose epinephrine compared with standard-dose epinephrine on survival is uncertain
Epinephrine (high dose)	Epinephrine plus vasopressin	1.03 (0.62-1.72)	Very low[d,e]	The effect of high-dose epinephrine compared with epinephrine plus vasopressin on survival is uncertain
Epinephrine (high dose)	Vasopressin	0.81 (0.51-1.29)	Very low[d,e]	The effect of high-dose epinephrine compared with vasopressin on survival is uncertain
Epinephrine (standard dose)	Vasopressin	0.85 (0.59-1.20)	Low[e]	The no difference in survival may exist between standard-dose epinephrine and vasopressin
Epinephrine plus vasopressin	Epinephrine (standard dose)	0.93 (0.61-1.41)	Low[e]	No difference in survival may exist between epinephrine plus vasopressin and standard-dose epinephrine
Epinephrine plus vasopressin	Vasopressin	0.79 (0.46-1.35)	Low[e]	No difference in survival may exist between epinephrine plus vasopressin and vasopressin alone

Data are presented as OR (95% CI). GRADE = Grading of Recommendations Assessment, Development, and Evaluation.
[a]Imprecision incorporated only at network level, not at direct or indirect.
[b]Lowered for inconsistency.
[c]Lowered for imprecision.
[d]Lowered for risk of bias of included trials.
[e]Lowered two levels for imprecision.

the number of survivors with good and poor neurologic outcomes, but ultimately its effect may be relatively minimal when compared with other interventions (such as bystander CPR and automated external defibrillation) that are used early in the course of CPR.[59] We see this reflected in the important subgroup analyses showing divergent effects of standard-dose epinephrine among patients with initial shockable vs nonshockable rhythms. In patients with initial shockable rhythms, we found no benefit of standard-dose epinephrine in improving overall survival, with the direction of the point estimate suggesting potential harm. This is consistent with observational evidence of patients with shockable IHCA, which shows an association between early epinephrine and poor outcomes.[60,61] In such patients, the potential harms of epinephrine on brain perfusion may dominate over any benefits,[57] and therefore focus should be toward early defibrillation, which has demonstrated efficacy.[62] The upcoming EpiDOSE RCT[63] will explore whether a lower cumulative dose of epinephrine might capture the benefits of standard-dose epinephrine, while avoiding the potential harms in patients with shockable rhythms. By contrast, we found that standard-dose epinephrine improved overall survival among patients with nonshockable rhythms. This may be because many patients with pulseless electrical activity or early asystole in fact may be profoundly hypotensive or severely bradycardic and not truly in cardiac arrest, and therefore could benefit from a vasopressor such as epinephrine (with chronotropic and inotropic effects).[64] These

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TABLE 4] Network Estimates Evaluating the Efficacy of Pharmacologic Agents for Survival With Good Functional Outcome After Out-of-Hospital Cardiac Arrest

Intervention 1	Intervention 2	Network Estimate[a]	GRADE	Narrative Summary
Epinephrine (standard dose)	Placebo or no treatment	0.95 (0.73-1.24)	Low[b,c]	Standard-dose epinephrine may have no effect on survival with good function outcome compared with no treatment
Epinephrine (high dose)	Placebo or no treatment	0.91 (0.58-1.41)	Very low[b,c,d]	The effect of high-dose epinephrine compared with no treatment on survival with good functional outcome is uncertain
Epinephrine plus vasopressin	Placebo or no treatment	0.55 (0.25-1.21)	Low[b,c]	Epinephrine plus vasopressin may decrease survival with good functional outcome compared with no treatment
Vasopressin	Placebo or no treatment	0.99 (0.51-1.91)	Very low[b,e]	The effect of vasopressin compared with no treatment on survival with good functional outcome is uncertain
Epinephrine (high dose)	Epinephrine (standard dose)	0.96 (0.67-1.36)	Low[b,c]	High-dose epinephrine may have no effect on survival with good functional outcome compared with standard-dose epinephrine
Epinephrine (high dose)	Epinephrine plus vasopressin	1.66 (0.73-3.80)	Very low[d,e]	The effect of high-dose epinephrine compared with epinephrine plus vasopressin on survival with good functional outcome is uncertain
Epinephrine (high dose)	Vasopressin	0.92 (0.46-1.86)	Very low[d,e]	The effect of high-dose epinephrine compared with vasopressin on survival with good functional outcome is uncertain
Epinephrine (standard dose)	Vasopressin	0.96 (0.52-1.76)	Low[e]	Standard-dose epinephrine may have no effect on survival with good functional outcome compared with vasopressin
Epinephrine plus vasopressin	Epinephrine (standard dose)	0.58 (0.27-1.22)	Low[e]	Standard-dose epinephrine may improve survival with good functional outcome compared with epinephrine plus vasopressin
Epinephrine plus vasopressin	Vasopressin	0.55 (0.21-1.46)	Low[e]	Vasopressin may improve survival with good functional outcome compared with epinephrine plus vasopressin

Data are presented as OR (95% CI). GRADE = Grading of Recommendations Assessment, Development, and Evaluation.
[a]Imprecision incorporated only at network level, not at direct or indirect.
[b]Lowered for inconsistency.
[c]Lowered for imprecision.
[d]Lowered for risk of bias of included studies.
[e]Lowered two levels for imprecision.

conflicting findings highlight the need to analyze patients with shockable and nonshockable rhythms separately in OHCA studies. The most recent International Liaison Committee on Resuscitation guidelines endorse a strong recommendation for the early use of epinephrine in nonshockable OHCA and a weak recommendation in shockable OHCA when defibrillation has been unsuccessful, in keeping with our findings.[4] Other organizations should consider adopting similar nuance within their guidelines regarding the approach to epinephrine use during OHCA.

Finally, the network meta-analysis design enabled us to compare the relative efficacy of these therapies against each other, which is particularly important because current OHCA guidelines specify epinephrine dosing of 1 mg and do not advocate for adjunctive dosing of other agents.[2,4] We found moderate-certainty evidence supporting higher-dose epinephrine over standard-dose epinephrine in increasing ROSC and survival to hospital admission. However, compared with standard-dose epinephrine, the effect of higher-dose epinephrine on survival with good functional outcome was uncertain.

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TABLE 5] Network Estimates Evaluating the Efficacy of Pharmacologic Agents Among Subgroups of Patients With Shockable and Nonshockable Out-of-Hospital Cardiac Arrest

Treatment 1	Treatment 2	ROSC		Survival to Admission		Survival to Discharge	
		Shockable Cardiac Arrest	Nonshockable Cardiac Arrest	Shockable Cardiac Arrest	Nonshockable Cardiac Arrest	Shockable Cardiac Arrest	Nonshockable Cardiac Arrest
Epinephrine (standard dose)	Placebo or no treatment	1.87 (1.20-2.45)	6.06 (4.71-7.79)	1.35 (0.73-2.52)	3.94 (2.61-5.95)	0.85 (0.39-1.85)	2.10 (1.21-3.63)
Epinephrine (high dose)	Placebo or no treatment	1.30 (0.69-2.45)	6.54 (4.54-9.44)	1.14 (0.43-3.04)	5.11 (2.59-10.08)	0.52 (0.16-1.63)	1.87 (0.86-4.07)
Epinephrine plus vasopressin	Placebo or no treatment	2.16 (0.68-6.87)	5.92 (3.04-11.51)	1.43 (0.31-6.59)	3.37 (1.77-6.40)	N/A	1.66 (0.69-3.98)
Vasopressin	Placebo or no treatment	2.22 (1.10-4.50)	6.25 (4.28-9.13)	2.10 (0.83-5.28)	4.91 (2.73-8.84)	1.51 (0.44-5.16)	2.68 (1.22-5.92)
Epinephrine (high dose)	Epinephrine (standard dose)	0.70 (0.44-1.09)	1.08 (0.80-1.46)	0.84 (0.39-1.80)	1.30 (0.76-2.23)	0.61 (0.26-1.41)	0.89 (0.51-1.55)
Epinephrine (high dose)	Epinephrine plus vasopressin	0.60 (0.19-1.92)	1.11 (0.56-2.20)	0.80 (0.16-3.91)	1.52 (0.75-3.09)	N/A	1.13 (0.47-2.71)
Epinephrine (high dose)	Vasopressin	0.59 (0.28-1.23)	1.05 (0.68-1.60)	0.54 (0.20-1.51)	1.04 (0.53-2.03)	0.34 (0.10-1.20)	0.70 (0.32-1.54)
Epinephrine (standard dose)	Vasopressin	0.84 (0.48-1.48)	0.97 (0.73-1.28)	0.65 (0.33-1.28)	0.80 (0.54-1.19)	0.56 (0.22-1.42)	0.78 (0.44-1.38)
Epinephrine plus vasopressin	Epinephrine (standard dose)	0.97 (0.29-3.26)	0.98 (0.53-1.81)	1.06 (0.26-4.27)	0.86 (0.54-1.36)	N/A	0.79 (0.40-1.56)

Data are presented as Network estimate (95% CI). ROSC = Return of spontaneous circulation.

Similarly, the combination of vasopressin with epinephrine did not improve ROSC or hospital admission over standard-dose epinephrine alone. Taken together, our work supports the current 1-mg dosing of epinephrine and does not provide evidence that higher doses of epinephrine or adjunctive treatment with vasopressin improve patient-centered outcomes.

This review has several strengths, including a broad search (without language restriction) and a preregistered protocol. We evaluated the most current available randomized data and exclusively focused our analyses on patients with OHCA. We used the GRADE standard to assess the certainty in effect estimates and conducted subgroup analyses among patients with shockable and nonshockable rhythms to provide further granularity to our conclusions. Our results also showed minimal statistical heterogeneity, with no incoherence. However, the study also has important limitations. First, 99.2% of the patients included in this review came from RCTs that enrolled patients regardless of the initial rhythm. We did try to overcome this heterogeneity through subgroup analyses comparing patients with shockable and nonshockable rhythms separately. However, we were unable to evaluate functional outcome in these subgroups. Second, data were insufficient to enable more granular network meta-analyses (such as those comparing pulseless electrical activity with asystole) or to evaluate longer-term functional status, and these subpopulations and outcomes warrant further study. In addition, few of the studies presented data on serious adverse events associated with the randomized agents. The included studies were conducted over several decades and across multiple continents, and this could result in substantial variability in prehospital systems, CPR protocols, defibrillation protocols, quality of CPR provided, and treatment after ROSC. We were unable to account for improvements in system care such as emergency medical services response time, rates of bystander CPR, and use of public access defibrillation, because these were reported inconsistently across the included trials. In trials involving high-dose epinephrine, variability in the dose selected was reported. Such sources of clinical heterogeneity must be considered when evaluating the different conclusions of the various trials. However, as mentioned, we did not find significant statistical heterogeneity, suggesting that such clinical heterogeneity across trials likely did not translate into important differences in effect. Third, one of our included trials was a secondary analysis of an initial trial,[45] and although randomization largely was preserved in this analysis, we cannot rule out the potential for selection bias. Although we sought to perform a subgroup analysis of only studies at low risk of bias, data were insufficient for NMA. However, risk of bias is incorporated into GRADE certainty ratings. Finally, although we included only RCTs that protocolized the use of epinephrine, most did not protocolize use of vasopressin, suggesting possible issues with transitivity. Although it is important to note that most trials, particularly PARAMEDIC-2,[47] did not allow for vasopressin administration in the prehospital setting, conclusions related to the use of vasopressin alone should be interpreted with caution.

Interpretation

Compared with placebo or no treatment, OHCA resuscitation with standard-dose epinephrine, high-dose epinephrine, epinephrine plus vasopressin, and vasopressin alone all increase ROSC and survival to hospital admission. However, none of these treatments may be associated with improved survival to hospital discharge or survival with good functional outcome. No benefit in these patient-centered outcomes was seen with high-dose epinephrine compared with standard-dose epinephrine. Finally, compared with placebo or no treatment, standard-dose epinephrine increased survival to hospital discharge among patients with nonshockable rhythms, but not those with shockable rhythms.

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Additional information: The e-Figures and e-Tables are available online under "Supplemental Data."

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