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TITLE: Epinephrine in Out-of-Hospital Cardiac Arrest – A Network Meta-Analysis and Subgroup Analyses of Shockable and Non-Shockable Rhythms

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Dr. Shannon M. Fernando has no conflicts to report.
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TAKE HOME POINT:

STUDY QUESTION: What is the comparative efficacy and safety of standard dose epinephrine, high dose epinephrine, epinephrine plus vasopressin, and placebo/no treatment in improving outcomes following out-of-hospital cardiac arrest (OHCA)?

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

ABSTRACT

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 is the comparative efficacy and safety of standard dose epinephrine, high dose epinephrine, epinephrine plus vasopressin, and placebo/no treatment in improving outcomes following OHCA?

STUDY DESIGN AND METHODS: Systematic review and network meta-analysis of randomized controlled trials. We searched six databases from inception to June 2022 for randomized controlled trials evaluating epinephrine use during OHCA resuscitation. We performed frequentist random-effects network meta-analysis, and present odds ratios (OR) and 95% confidence intervals (CI). We used GRADE 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/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/no treatment. However, none of these agents may increase survival to discharge or survival with good functional outcome, as compared with placebo/no treatment. Compared with placebo/no treatment, standard dose epinephrine improved survival to discharge among patients with non-shockable 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 non-shockable rhythm, but not those with shockable rhythm.

REGISTRATION: Center for Open Science: (LINK ANONYMIZED).

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) remains an important cause of morbidity and mortality worldwide. Incidence rates of OHCA vary between 30-60 per 100,000 person-years, and only 11-30% 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 of epinephrine (adrenaline) during adult cardiopulmonary resuscitation (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 and aortic diastolic pressure, and cardiac contractility.[5,6] This physiologic rationale was supported by early non-human studies,[7] and use of epinephrine is common in OHCA treatment worldwide.[8]

Despite the widespread use of epinephrine in OHCA, there is limited high certainty data supporting its efficacy in improving patient-centred outcomes.[9] While some observational data has 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-centred outcomes.[12] As such, evaluation of randomized evidence surrounding the use of epinephrine is a priority, particularly in relation 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 to 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 in a particular condition, and generate indirect estimates of effect between treatments that have never been compared previously. The purpose was to evaluate the relative efficacy and safety of four pharmacological treatments in adult OHCA patients: standard dose epinephrine (1mg or 0.01-0.02mg/kg), high dose epinephrine (single dose ≥ 5mg or ≥ 0.1mg/kg), the combination of standard dose epinephrine and vasopressin, and vasopressin alone (without epinephrine), as compared to each other and placebo/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 non-shockable OHCA. We hypothesized that epinephrine would be beneficial in non-shockable OHCA, but not shockable OHCA.

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 (LINK ANONYMIZED).

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 to June 24, 2022. In consultation with the review authors, an experienced health sciences librarian developed the search strategy (***Supplemental Figure 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 on epinephrine in OHCA.[13,15,16]

Study Selection

Two reviewers (ANONYMOUS) independently screened titles and abstracts using Covidence (Melbourne, Australia). 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 non-traumatic OHCA (with any initial cardiac rhythm and regardless of presumed underlying etiology); 3) randomized patients to a treatment arm that protocolized the use of epinephrine (e.g., either standard dose epinephrine, high dose epinephrine, the combination of epinephrine and vasopressin, vasopressin alone [without epinephrine], or placebo/no intravascular drug treatment); and 4) reported at least one of the outcomes of interest (see below). We excluded: 1) trials that exclusively used non-intravascular routes for epinephrine administration (e.g., via tracheal tube, intraosseous, or intramuscular); 2) secondary analyses that evaluated subgroups of patients enrolled in larger RCTs; and 3) trials that used a non-randomized control cohort. In RCTs enrolling patients with both OHCA and in-hospital cardiac arrest (IHCA), we evaluated only OHCA patients. When data on OHCA patients was not presented separately, we contacted authors to obtain primary data from OHCA patients only.

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 post-discharge), and survival with good functional outcome at discharge (or the latest time point reported up until 6 months post-discharge). Good functional outcome was defined on the basis of any of the following: 1) modified Rankin Scale (mRS) score of 0 (no symptoms at all) to 3 (moderate disability); 2) Cerebral Performance Categories (CPC) 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 (ANONYMOUS) used a pre-designed data extraction form to collect the following variables: author information, publication year, eligibility criteria, and number of patients (***Supplemental Table 1***). Two investigators (ANONYMOUS) independently collected data related to descriptions of interventions and outcomes. Disagreements were resolved through discussion and consensus.

Risk of Bias Assessment

Two reviewers (ANONYMOUS) 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 odds ratios (OR) and corresponding 95% confidence intervals (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 the: 1) availability of evidence (e.g., number of trials, number of interventions); 2) homogeneity of study designs, patients, and characteristics of interventions across the body of evidence (transitivity assumption); 3) structural properties of the network of evidence (e.g., connectivity); and 4) coherence in 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 or more RCTs were available.[28] In sparse networks, using a random-effects model with common-

heterogeneity assumption for network meta-analysis can lead to confidence intervals 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 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 16 (StataCorp, College Station, TX, USA).

Subgroup Analyses

Initial rhythm has important prognostic associations with outcomes following 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 non-shockable rhythm (pulseless electrical activity [PEA] or asystole). We then conducted separate network meta-analyses among these subgroups. We hypothesized that epinephrine would be beneficial in non-shockable 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 (***Figure 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 OHCA and IHCA patients,[50] but we included only OHCA patients in meta-analysis. Characteristics of the included trials are shown in ***Supplemental Tables 2-3***. Risk-of-bias assessments are shown in ***Supplemental Table 4***. Seven of the included trials were deemed to have at least some risk of bias,[34,35,37,39,44,45] while 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.[44,45,48] Some concerns were noted with regard to allocation concealment in three trials,[34,39,44] and allocation sequencing in three trials.[35,39,44]

Return of Spontaneous Circulation

Summary of findings, including network estimates, for ROSC is shown in ***Table 1***. Network diagram, SUCRA table, and estimates of incoherence are shown in ***Supplemental Table 4***. Compared with placebo/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 incidence of ROSC (all high certainty). Compared to standard dose epinephrine, high dose epinephrine probably increases the incidence of ROSC (OR 1.16 [95% CI: 1.04-1.29], moderate certainty), while epinephrine plus vasopressin probably has 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 ***Supplemental Table 6***. As compared with placebo/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 increase survival to hospital admission following OHCA (all high certainty). High dose epinephrine probably increases survival to hospital admission, compared to standard dose epinephrine (OR 1.18 [95% CI: 1.04-1.34], moderate certainty). There are probably no important differences in survival to hospital admission 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 ***Supplemental Table 6***. GRADE certainty was limited due to imprecision and low incidence of the outcome. Compared to placebo/no treatment, there may be no important difference in survival to hospital discharge with standard dose epinephrine (OR 1.14 [95% CI: 0.90-1.44], low certainty). There was 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]) in improving survival to hospital discharge, compared to placebo/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 ***Supplemental Table 8***. GRADE certainty was limited due to imprecision and low incidence of the outcome. Compared to placebo/no treatment, we found standard dose epinephrine may have 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 to placebo/no treatment is uncertain (very low certainty). Finally, high dose epinephrine

may have no effect on survival with good functional outcome, compared to standard dose epinephrine (OR 0.96 [95% CI: 0.67-1.36], low certainty).

Subgroup Analyses – Shockable vs. Non-shockable Initial Rhythm

We separately compared patients with non-shockable rhythms and those with shockable rhythms, as extracted from the included trials (***Table 5***). Network plots and SUCRA tables are shown in ***Supplemental Tables 9-14***. Among patients with initial non-shockable 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]). There was insufficient data 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.

DISCUSSION

The use of epinephrine is common during OHCA resuscitation and is currently recommended by clinical practice guidelines from the American Heart Association (AHA) and the European Resuscitation Council, based on the consensus on science and treatment recommendations of the International Liaison Committee on Resuscitation (ILCOR).[2-4] However, there is mixed evidence on its efficacy. Traditional meta-analyses have largely shown potential benefit of standard dose epinephrine over placebo in

improving survival, but without improvement in functional outcomes.[13-16] This controversy was further fueled by the PARAMEDIC-2 trial,[47] which found 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 effective in improving survival – a treatment that has only been used in the IHCA population, and has since been shown to improve rate of ROSC, but not survival or neurological 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/no treatment, but the network meta-analysis design allowed us to leverage additional trials, and compare additional treatments that have never been tested against placebo/no treatment or each other in a RCT. Our results are mostly consistent with the PARAMEDIC-2 trial. While 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 epidemiology and outcome, we deliberately only included patients with OHCA, and therefore it is unknown as to 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] There is some experimental evidence showing that epinephrine may cause harm by worsening brain tissue perfusion, suggesting 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 epinephrine improves cerebral oxygenation and metabolism.[57,58] Most likely, epinephrine does increase 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 our important subgroup analyses showing divergent effects of standard dose epinephrine among patients with initial shockable vs. non-shockable 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 might dominate over any benefits,[57] and therefore focus should be towards early defibrillation, which has demonstrated efficacy.[62] The upcoming EpiDOSE RCT (NCT03826524) will explore whether lower cumulative dose epinephrine might capture the benefits of standard-dose epinephrine, while avoiding the potential harms in patients with shockable rhythms. By contrast, we found standard dose epinephrine improved overall survival among patients with non-shockable rhythms. This might be because many patients with PEA or early

asystole may in fact be profoundly hypotensive or severely bradycardic and not truly in cardiac arrest, and therefore could benefit from a vasopressor such as epinephrine (with chrono- and inotropic effects).[63] These conflicting findings highlight the need to separately analyze patients with shockable and non-shockable rhythms in OHCA studies. The most recent ILCOR guidelines endorse a 'strong recommendation' for the early use of epinephrine in non-shockable OHCA, and a 'weak recommendation' in shockable OHCA where defibrillation has been unsuccessful, in keeping with our findings.[4] Other organizations should consider adopting similar nuance within their guidelines with regard to 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 as current OHCA guidelines specify epinephrine dosing of 1mg, 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 to standard dose epinephrine, the effect of higher dose epinephrine on survival with good functional outcome was uncertain. 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 1mg dosing of epinephrine, and does not provide evidence that higher doses of epinephrine, or adjunctive treatment with vasopressin, improves patient-centred outcomes.

This review has several strengths, including a broad search (without language restriction), and a pre-registered protocol. We evaluated the most current available

randomized data and exclusively focused our analyses on OHCA patients. We used GRADE to assess the certainty in effect estimates, and conducted subgroup analyses among patients with shockable and non-shockable rhythms to provide further granularity to our conclusions. Our results also had minimal statistical heterogeneity, with no incoherence. However, there are also important limitations. First, 99.2% of the patients included in this review came from RCTs that enrolled patients regardless of their initial rhythm. We did try to overcome this heterogeneity through subgroup analyses comparing patients with shockable and non-shockable rhythms separately. However, we were unable to evaluate functional outcome in these subgroups. Second, there was insufficient data to enable more granular network meta-analyses (such as those comparing PEA 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 post-ROSC treatment. 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, as these were inconsistently reported across the included trials. In trials involving high dose epinephrine, there was variability in the dose selected. 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 while randomization was largely preserved in this analysis, we cannot rule out potential for selection bias. While we sought to perform a subgroup analysis of only studies at low risk of bias, there was insufficient data for NMA. However, risk of bias is incorporated into GRADE certainty ratings. Finally, while we included only RCTs that protocolized the use of epinephrine, most did not protocolize use of vasopressin, suggesting possible issues with transitivity. While it is important to note that the majority of trials, particularly PARAMEDIC-2,[47] did not allow for vasopressin administration in the pre-hospital setting, conclusions related to the use of vasopressin alone should be interpreted with caution.

CONCLUSIONS

Compared to placebo/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-centred outcomes was seen with high dose epinephrine, compared to standard dose epinephrine. Finally, compared to placebo/no treatment, standard dose epinephrine increased survival to hospital discharge among patients with non-shockable rhythms, but not those with shockable rhythms.

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Supplemental Figure 1: Electronic Search Strategies.

Databases Searched:

- EMBASE Classic + Embase
- PubMed/Medline
- Scopus
- Web of Science
- Cochrane Central Register of Controlled Trials (CENTRAL)

EMBASE Classic + EMBASE

	Search Strategy	Results
1	exp Heart Arrest/	111767
2	cardiac arrest.tw.	62062
3	cardiovascular arrest.tw.	107
4	heart arrest.tw.	397
5	cardiopulmonary arrest.tw.	3952
6	cardiopulmonary resuscitation.mp.	26118
7	asystole.mp.	8001
8	pulseless electrical activity.mp.	2140
9	advanced cardiac life support.mp.	1957
10	ACLS.tw.	2238
11	ventricular fibrillation/	17495
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	148005
13	exp Epinephrine/	22302
14	exp Vasopressin/	36112
15	(Epinephrine or vasopressin* or adrenaline).tw.	102833
16	Injections, Intravenous/	365616
17	13 or 14 or 15 or 16	487733
18	12 and 17	9577

PubMed/MEDLINE

	Search Strategy	Results
1	exp Heart Arrest/	53971
2	cardiac arrest.tw.	38937
3	cardiovascular arrest.tw.	74
4	heart arrest.tw.	597
5	cardiopulmonary arrest.tw.	2584
6	cardiopulmonary resuscitation.mp.	28206
7	asystole.mp.	4058
8	pulseless electrical activity.mp.	1035
9	advanced cardiac life support.mp.	2001
10	ACLS.tw.	1218
11	ventricular fibrillation/	17658
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11	98377
13	exp Epinephrine/	56896
14	exp Vasopressin/	36669
15	(Epinephrine or vasopressin* or adrenaline).tw.	85444
16	Injections, Intravenous/	54097
17	13 or 14 or 15 or 16	191908
18	12 and 17	3080

Supplemental Table 1: Standardized Data Extraction Sheet.

Data to be Extracted	Notes to Reviewer
Basic Study Information	
Study Title	
Journal/Conference	
Conference Abstract vs. Full-text	
Year of Publication	
Language	
Author	List first author only
Correspondence Email	
Randomized Trial?	If "No" – Exclude
Parallel vs. Crossover vs. Cluster	
Number of Sites	
Country/Countries of Study	
Eligibility Assessment	
Does the trial include adult patients (i.e. ≥ 16 years of age)?	If "No" – Exclude
Was the trial conducted in patients with non-traumatic out-of-hospital cardiac arrest (regardless of initial rhythm or presumed etiology of arrest)	If "No" – Exclude
Did the trial randomize patients to a treatment arm that protocolized the use of epinephrine? (e.g., standard-dose epinephrine, high-dose epinephrine, epinephrine + vasopressin, etc.).	If "No" – Exclude
Are any of the following outcomes evaluated: 1) Return of spontaneous circulation (ROSC); 2) Survival to hospital admission; 3) Survival to hospital discharge (or the latest time period up to 6 months); or 4) Survival to hospital discharge (or the latest time period up to 6 months) with good functional outcome?	If "No" – Exclude
Did the trial exclusively use non-intravenous routes for epinephrine administration (e.g. via endotracheal tube or intramuscular)?	If "Yes" – Exclude
Is the study a secondary analysis or includes only a subpopulation of a previous randomized trial?	If "Yes" – Exclude
Did the study include a non-randomized control cohort?	If "Yes" – Exclude
Trial Characteristics	
Inclusion Criteria	

Exclusion Criteria	
Initial rhythm	
Witnessed cardiac arrest	
Bystander cardiopulmonary resuscitation	
Were elderly patients included?	
Were pregnant patients included?	
Were patients with any other co-morbidity included/excluded?	
Treatment 1	
Treatment 2	
Treatment 3 (if applicable)	
Risk of Bias Assessment	
How were patients randomized?	
In either the intervention or the control group, were there any deviations from the protocol?	
Were treating clinicians blinded to group assignment? Were outcome assessors blinded to group assignment?	
Was there any missing outcome data?	
Were the outcome measures objective?	
Were all important pre-specified outcomes presented?	
Any other bias noted?	
Outcome #1	
Outcome being evaluated	e.g. Return of spontaneous circulation (ROSC)
Dichotomous or continuous outcome?	
Treatment 1: N analyzed	
Treatment 1: Number of Events/Mean	
Treatment 2: N analyzed	
Treatment 2: Number of Events/Mean	
Comments	
Outcome #2	
Outcome being evaluated	e.g. Survival
Dichotomous or continuous outcome?	
Treatment 1: N analyzed	
Treatment 1: Number of Events/Mean	
Treatment 2: N analyzed	
Treatment 2: Number of Events/Mean	
Comments	
Author Contact	
Contact author?	If more information needed, indicate here to contact author

Supplemental Table 2: Characteristics of the 18 randomized clinical trials.

	Overall (18 studies, *n* = 21,594)	
Description	Number of Studies (%)	Number of Patients (%)
Continent of Study		
Europe	8 (44.4)	16,875 (78.1)
North America	6 (33.3)	3,022 (14.0)
Asia	3 (16.7)	1,163 (5.4)
Australia	1 (5.6)	534 (2.5)
Year of Publication		
1990-1994	4 (22.2)	2,557 (11.8)
1995-1999	5 (27.8)	4,368 (20.2)
2000-2004	1 (5.6)	1,186 (5.5)
2005-2009	2 (11.1)	3,230 (15.0)
2010-2014	4 (22.2)	2,139 (9.9)
2015-2019	2 (11.1)	8,114 (37.6)
Sites		
Single Center	8 (44.4)	1,994 (9.2)
Multicenter	10 (55.6)	19,600 (90.8)
Initial Rhythm		
Ventricular Fibrillation	1 (5.6)	40 (0.2)
Ventricular Fibrillation/Asystole	1 (5.6)	140 (0.6)
Any	16 (88.9)	21,414 (99.2)
Interventions Studied		
Standard Dose Epinephrine	18 (100.0)	10,711 (49.6)
High Dose Epinephrine	7 (38.9)	3,307 (15.3)
Standard Dose Epinephrine + Vasopressin	4 (22.2)	1,673 (7.7)
Vasopressin Alone (Without Epinephrine)	4 (22.2)	1,161 (5.4)
Placebo/No Treatment	3 (16.7)	4,742 (22.0)

Supplemental Table 3: Detailed Characteristics of the 18 Included Studies.

Author (Trial Name)	Year	Journal	Sites	Country	Initial Rhythm	Inclusion Criteria	Exclusion Criteria	Treatment Arms	Outcomes	N	Mean Age	% Male
Brown	1992	N Engl J Med	6	United States	Any	>18 years; Cardiopulmonary arrest outside of the hospital	Pregnant; Traumatic arrest; Hypothermia; Drowning; Drug overdose; Primary respiratory arrest; ET tube could not be placed; Clear signs of irreversible arrest	1) Standard dose epinephrine (0.02mg/kg); 2) Higher dose epinephrine (0.2mg/kg)	ROSC; Successful resuscitation; Admission to hospital; Hospital mortality; Survival with good neurological outcome	1280	66	66.5
Callaham	1992	JAMA	1	United States	Any	>18 years; nontraumatic, normothermic cardiac arrest		1) Standard dose epinephrine (1mg); 2) Higher dose epinephrine (15mg)	ROSC; Successful resuscitation; Admission to hospital; Hospital mortality; Survival with good	556	65.5	69.1

									neurological outcome			
Callaway	1996	Am J Cardiol	1	United States	Any	>18 years; with out-of-hospital cardiac arrest requiring paramedic resuscitation	Traumatic arrest; Prisoner: Existing DNR; ROSC before randomization; No intravenous access	1) Standard dose epinephrine (1mg); 2) Standard dose epinephrine (1mg) and vasopressin (20 IU)	ROSC; 30-day survival; Survival with good neurological outcome	325	65.5	60.9
Choux	1995	Resuscitation	1	France	Any	>18 years; Cardiopulmonary arrest outside of the hospital	<18 years of age; Clear signs of irreversible cardiac arrest; Receipt of epinephrine prior to randomization	1) Standard dose epinephrine (1mg); 2) Higher dose epinephrine (15mg)	ROSC; Admission to hospital; Survival to discharge; Neurological outcome at 6 months	536	58.4	71.8
Ducros	2011	J Emerg Med	1	France	Any	>18 years; Cardiopulmonary arrest outside of the hospital; Initiation of BLS by police or fireighters	Unwitnessed cardiac arrest; Spontaneous ROSC before administration of vasopressor; No IV access; Pregnancy;	1) Standard dose epinephrine (1mg); 2) Standard dose epinephrine (1mg) and vasopressin (40 IU)	ROSC; Admission to hospital; Survival to discharge	30	58	83.3

							Traumatic injuries					
Ghafourian	2015	Recent Adv Cardiovasc Drug Discov	1	Iran	Any	>18 years; Cardiopulmonary arrest outside of the hospital	Pregnant; Exogenous steroid use	1) Standard dose epinephrine (1mg); 2) Standard dose epinephrine (1mg) and vasopressin (40 IU)	Survival at 7 days	100	Unknown	73.6
Gueugniaud	1998	N Engl J Med	12	France; Belgium	Any	>18 years; Cardiopulmonary arrest outside of the hospital	<18 years of age; Clear signs of irreversible cardiac arrest; Receipt of epinephrine prior to randomization	1) Standard dose epinephrine (1mg); 2) Higher dose epinephrine (5mg)	ROSC; Admission to hospital; Survival to discharge; Neurological outcome at discharge	3327	65.3	69.9
Gueguniaud	2008	N Engl J Med	31	France	Any	>18 years; Cardiopulmonary arrest outside of the hospital	<18 years of age; Successful defibrillation without administration of a vasopressor; Traumatic cardiac arrest;	1) Standard dose epinephrine (1mg); 2) Standard dose epinephrine (1mg) and vasopressin (40 IU)	ROSC; Admission to hospital; Survival to discharge; Neurological outcome at discharge	2894	61.5	73.5

							Pregnancy; Documented terminal illness; Presence of a DNR; Clear signs of irreversible cardiac arrest					
Jacobs	2014	Resuscitation	>1	Australia	Any	>18 years; Cardiopulmonary arrest outside of the hospital		1) Standard dose epinephrine (1mg); 2) Placebo/No treatment	ROSC; Admission to hospital; Survival to discharge; Neurological outcome at discharge	534	64.6	72.8
Lindner	1997	Lancet	1	Germany	VF	>18 years; Cardiopulmonary arrest outside of the hospital	<18 years of age; Traumatic cardiac arrest; Terminal illness; Pregnancy; Endotracheal administration of epinephrine	1) Standard dose epinephrine (1mg); 2) Vasopressin (40 IU)	ROSC; Admission to hospital; Survival to discharge	40	65	72.5
Mukoyama	2009	Resuscitation	1	Japan	Any	>18 years; Cardiopulmonary arrest outside of the hospital;	<18 years of age; No IV access; Vasopressors	1) Standard dose epinephrine (1mg);	Admission to hospital; Survival to discharge;	336	65.4	71.4

						Ongoing CPR on ER arrival	in the prehospital setting; Indications for cardipulmonary bypass; Terminal illness; DNR; Non-cardiac etiology	2) Vasopressin (40 IU)	Neurological outcome at discharge			
Olasveengen (post-hoc)	2012	Resuscitation	2	Norway	Any	>18 years; Cardiopulmonary arrest outside of the hospital; Non-traumatic; Not witnessed by EMS		1) Standard dose epinephrine (1mg); 2) Placebo/No treatment	ROSC; Admission to hospital; Survival to discharge; Neurological outcome at discharge	848	66	71.1
Ong	2012	Resuscitation	4	Singapore	Any	>16 years; Cardiopulmonary arrest outside of the hospital	Traumatic arrest; CPR contraindicated	1) Standard dose epinephrine (1mg); 2) Vasopressin (40 IU)	ROSC; Admission to hospital; Survival to discharge; Neurological outcome at discharge	727	64.7	67.6
Perkins	2018	N Engl J Med	>1	United Kingdom	Any	>16 years; Cardiopulmonary arrest outside of the hospital	Pregnancy; Age < 16 years; Cardiac arrest from anaphylaxis or	1) Standard dose epinephrine (1mg);	ROSC; Admission to hospital; Survival to discharge;	8014	69.7	64.8

							asthma; Administration of epinephrine before EMS arrival	2) Placebo/No treatment	Neurological outcome at discharge			
Polglase	1994	Am J Emerg Med	1	United States	Any	>18 years; Cardiopulmonary arrest outside of the hospital		1) Standard dose epinephrine (1mg); 2) Higher dose epinephrine (5mg)	ROSC; Admission to hospital; Survival to discharge	71	58	
Sherman	1997	J Hum Pharmacol Drug Ther	8	United States	VF or Asystole	>18 years; Cardiopulmonary arrest outside of the hospital	<18 years of age; Solid organ transplant; Not considered candidates for CPR; Pregnancy; No IV access	1) Standard dose epinephrine (0.01mg/kg); 2) Higher dose epinephrine (0.1mg/kg)	ROSC; Admission to hospital; Survival to discharge	140	66	55.7
Stiell	1992	N Engl J Med	2	Canada	Any	>16 years; Cardiopulmonary arrest outside of the hospital	<16 years of age; Terminal illness; No CPR for 15 minutes; Traumatic cardiac arrest;	1) Standard dose epinephrine (1mg); 2) Higher dose	ROSC; Admission to hospital; Survival to discharge; Neurologica	650	66.5	64.5

							Second cardiac arrest during same admission	epinephrine (7mg)	l outcome at discharge			
Wenzel	2004	N Engl J Med	44	Austria, Switzerland, Germany	Any	>18 years; Cardiopulmonary arrest outside of the hospital	<18 years of age; Successful defibrillation without administration of a vasopressor; Traumatic cardiac arrest; Pregnancy; Documented terminal illness; Presence of a DNR	1) Standard dose epinephrine (1mg); 2) Vasopressin (40 IU)	ROSC; Admission to hospital; Survival to discharge; Neurological outcome at discharge	1186	66.2	69.4

Supplemental Table 4: Quality Assessment for Risk of Bias of the 18 randomized trials.

Author (Year)	Journal	N	Arm 1	Arm 2	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Results
Brown (1992)	N Engl J Med	1280	Epinephrine (Standard)	Epinephrine (High-dose)	High[a]	Low	Low	Low	Low
Callaham (1992)	JAMA	556	Epinephrine (Standard)	Epinephrine (High-dose)	Some concerns[b]	Low	Low	Low	Low
Callaway (1996)	Am J Cardiol	325	Epinephrine (Standard)	Epinephrine + Vasopressin	Low	Low	Low	Low	Low
Choux (1995)	Resuscitation	536	Epinephrine (Standard)	Epinephrine (High-dose)	Low	Low	Low	Low	Low
Ducros (2011)	J Emerg Med	30	Epinephrine (Standard)	Epinephrine + Vasopressin	Low	Low	Low	Low	Low
Ghafourian (2015)	Recent Adv Cardiovasc Drug Discov	100	Epinephrine (Standard)	Epinephrine + Vasopressin	Some concerns[a,b]	Low	Low	Low	Low
Gueugniaud (1998)	N Engl J Med	3327	Epinephrine (Standard)	Epinephrine (High-dose)	Low	Low	Low	Low	Low

Gueugniaud (2008)	N Engl J Med	2894	Epinephrine (Standard)	Epinephrine + Vasopressin	Low	Low	Low	Low	Low
Jacobs (2014)	Resuscitation	534	Epinephrine (Standard)	Placebo/No Treatment	Low	Low	Low	Low	Low
Lindner (1997)	Lancet	40	Epinephrine (Standard)	Vasopressin	Low	Low	Low	Low	Low
Mukoyama (2009)	Resuscitation	336	Epinephrine (Standard)	Vasopressin	Some concerns[a,b]	Some concerns[c]	Low	Low	Low
Olasveengen (2012)	Resuscitation	848	Epinephrine (Standard)	Placebo/No Treatment	Low	High[c]	Low	Low	Low
Ong (2012)	Resuscitation	727	Epinephrine (Standard)	Vasopressin	Low	Low	Low	Low	Low
Perkins (2018)	N Engl J Med	8014	Epinephrine (Standard)	Placebo/No Treatment	Low	Low	Low	Low	Low
Polglase (1994)	Am J Emerg Med	71	Epinephrine (Standard)	Epinephrine (High-dose)	Some concerns[a,b]	High[c]	Low	Low	Low
Sherman (1997)	J Human Pharmacol Drug Ther	140	Epinephrine (Standard)	Epinephrine (High-dose)	Low	Low	Low	Low	Low

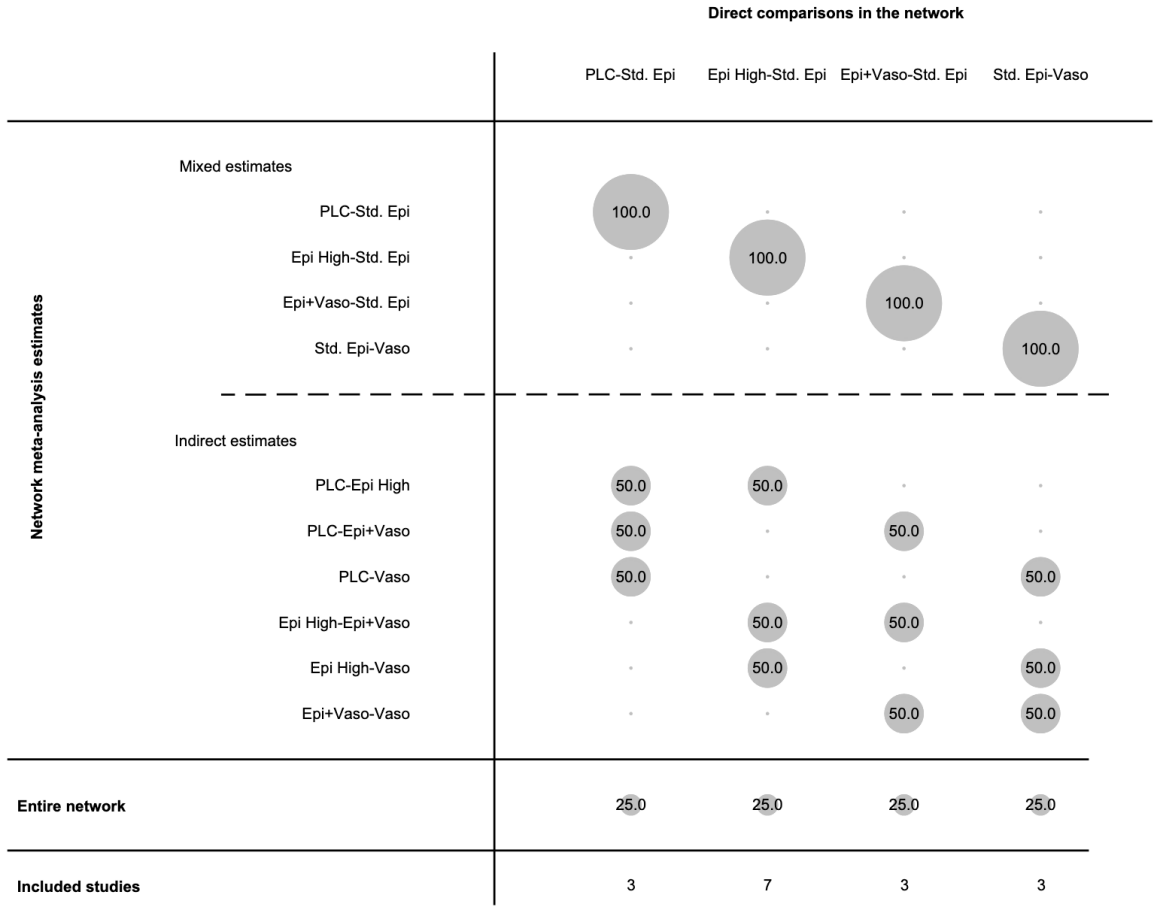
Stiell (1992)	N Engl J Med	650	Epinephrine (Standard)	Epinephrine (High-dose)	Low	Low	Low	Low	Low
Wenzel (2004)	N Engl J Med	1186	Epinephrine (Standard)	Vasopressin	Low	Low	Low	Low	Low

Adapted from Sterne et al., BMJ, 2019

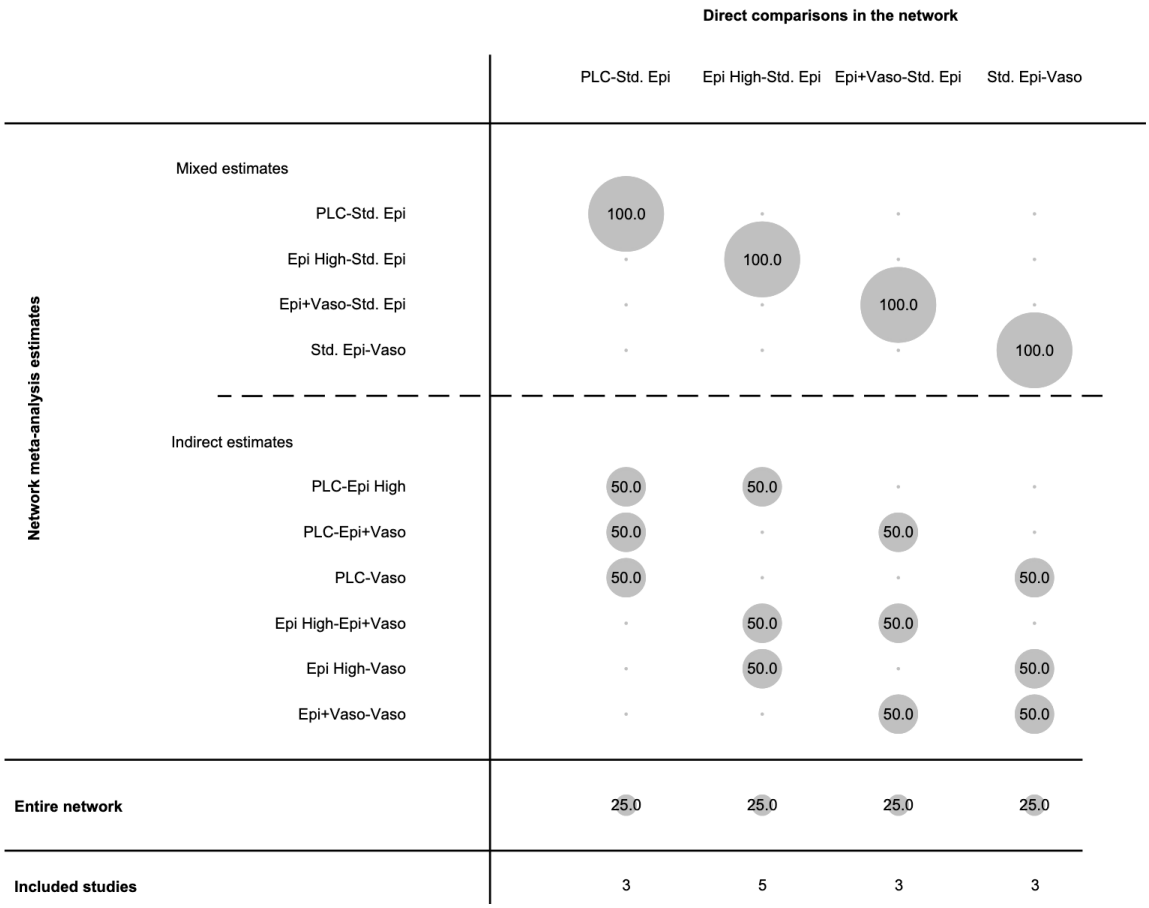
[a]Downrated due to concerns regarding allocation concealment
[b]Downrated due to concerns regarding allocation sequencing
[c]Downrated due to lack of information or concerns regarding blinding

Supplemental Figure 3: Contribution Matrices for Primary Outcomes.

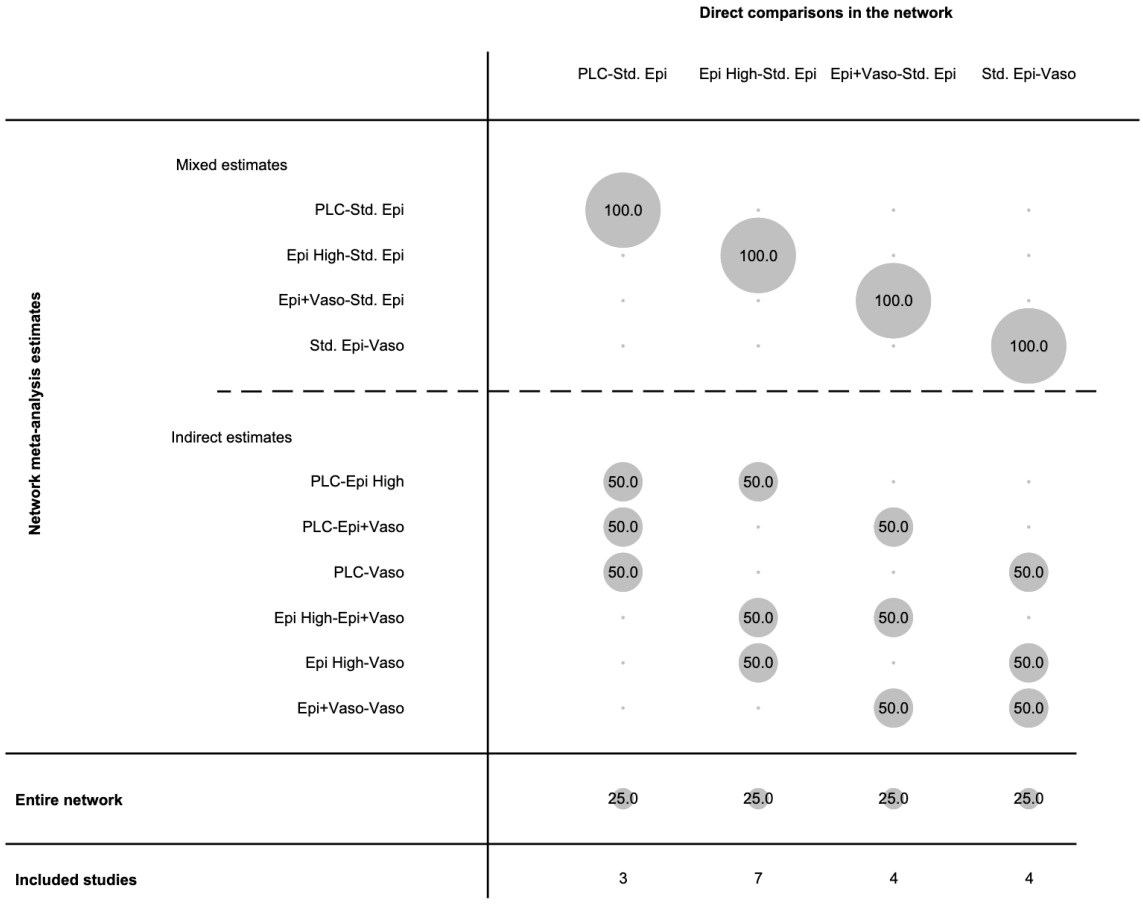
Return of Spontaneous Circulation



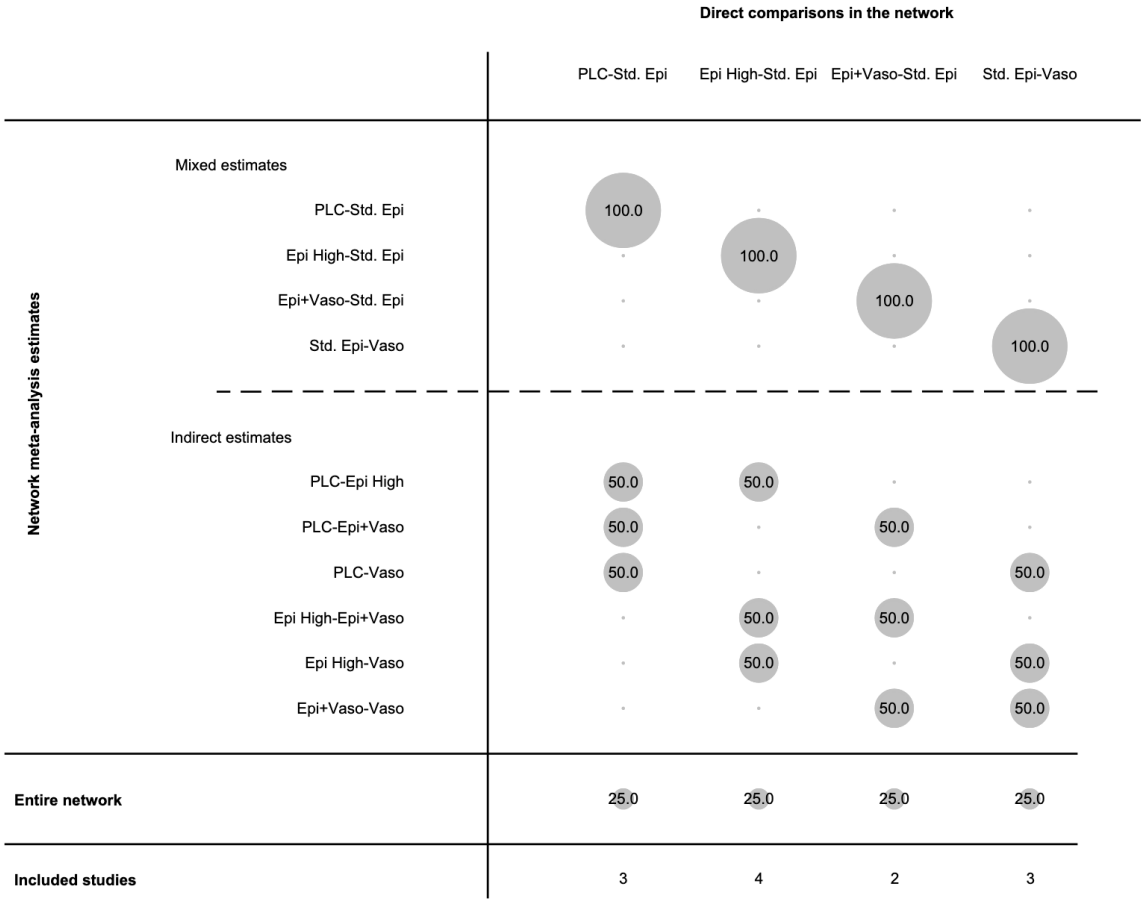
Survival to Hospital Admission



Survival to Discharge

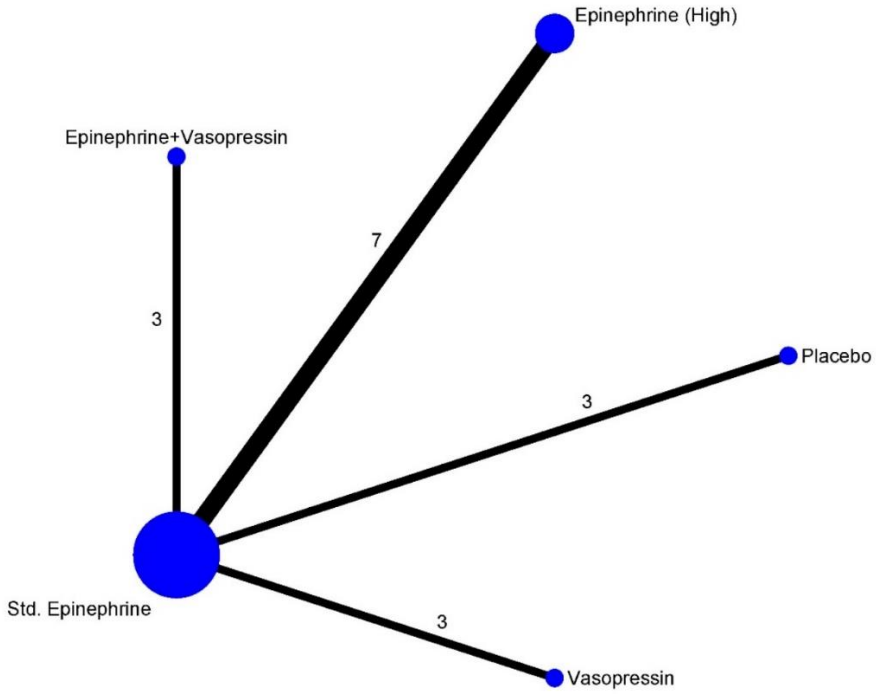


Survival with Good Functional Outcome



Supplemental Table 5: Network plot, Surface Under the Cumulative Ranking curve (SUCRA) and pairwise incoherence for return of spontaneous circulation (ROSC).

Network Plot



SUCRA and ranking probabilities for treatments

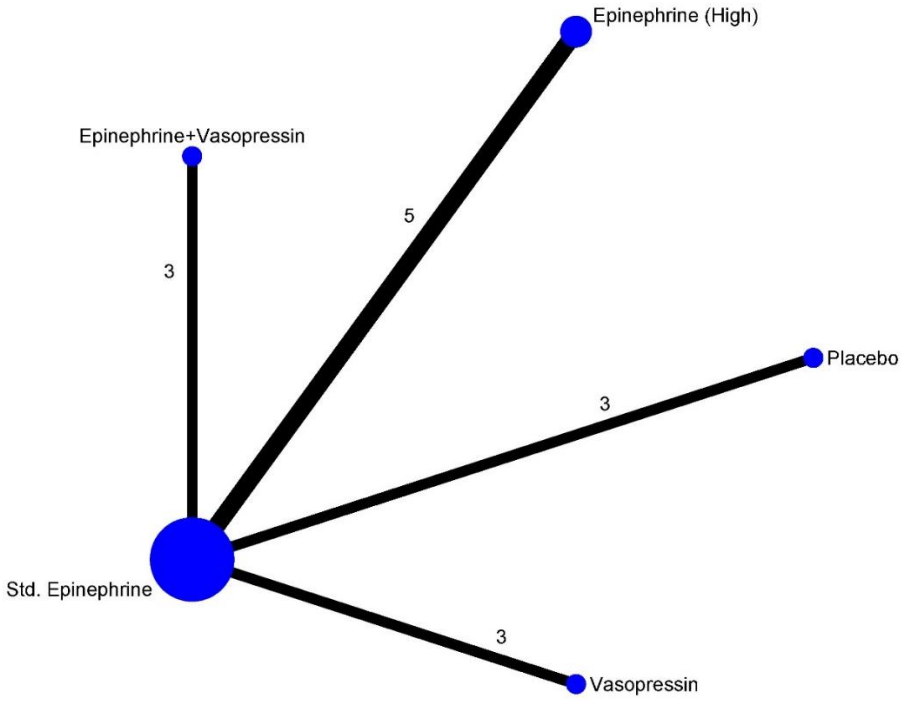
Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Epinephrine (High Dose)	98.2	93.4	1.1
Vasopressin	46.6	4.5	3.1
Epinephrine (Standard Dose)	59.3	0.2	2.6
Epinephrine + Vasopressin	45.9	1.9	3.2
Placebo	0.0	0.0	5.0

Direct and indirect estimates of effect and P value for pairwise incoherence

Comparison	Direct ES OR (95% CI)	I^2	Indirect ES OR (95% CI)	incoherence		P value for incoherence
				IF	SE log of IF	
Epi (high) vs Std. Epi*	1.15 (0.98, 1.35)	29.6	0.14 (0, .)	-2.146	585.723	0.997
Epi + Vasopressin vs Std. Epi*	0.96 (0.83, 1.12)	0.0	0.14 (0, .)	-1.881	805.655	0.998
Std. Epi vs Placebo*	2.65 (1.15, 6.14)	96.1	0.96 (0, .)	-1.029	199.179	0.996
Std. Epi vs Vasopressin*	0.98 (0.68, 1.40)	55.8	7.78 (0, .)	2.128	845.504	0.998

* All the evidence about these contrasts comes from the trials which directly compare them.

Supplemental Table 6: Network plot, Surface Under the Cumulative Ranking curve (SUCRA) and pairwise incoherence for survival to hospital admission.



SUCRA and ranking probabilities for treatments

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Vasopressin	94.9	82.2	1.2
Epinephrine (High)	79.0	17.7	1.8
Epinephrine (Standard)	45.3	0.0	3.2
Epinephrine + Vasopressin	30.8	0.1	3.8
Placebo	0.0	0.0	5.0

Direct and indirect estimates of effect and P value for pairwise incoherence

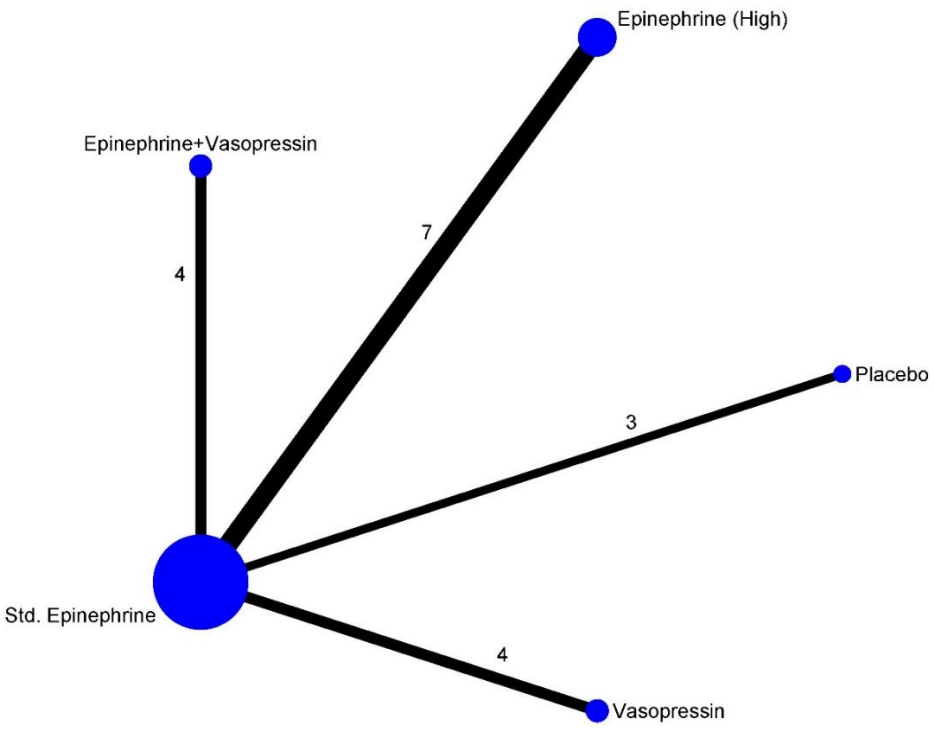
Comparison	Direct ES OR (95% CI)	I^2	Indirect ES OR (95% CI)	incoherence		P value for incoherence
				IF	SE log of IF	
Epi (high) vs Std. Epi*	1.19 (1.02, 1.39)	14.3	0.19 (0, .)	-1.892	748.621	0.998
Epi + Vasopressin vs Std. Epi*	0.93 (0.79, 1.10)	0.0	0.19 (0, .)	-1.503	802.786	0.999
Std. Epi vs Placebo*	2.25 (1.17, 4.34)	93.7	0.92 (0, .)	-0.913	226.543	0.997

Std. Epi vs Vasopressin*	0.70 (0.44, 1.09)	45.6	6.22 (0, .)	2.203	954.2449	0.998

* All the evidence about these contrasts comes from the trials which directly compare them.

Supplemental Table 7: Network plot, Surface Under the Cumulative Ranking curve (SUCRA) and pairwise incoherence for overall survival.

Network Plot



SUCRA and ranking probabilities for treatments

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Vasopressin	84.3	66.5	1.6
Epinephrine (High)	45.4	11.8	3.2
Epinephrine (Standard)	57.2	5.7	2.7
Epinephrine + Vasopressin	39.8	13.7	3.4
Placebo	23.3	2.3	4.1

Direct and indirect estimates of effect and P value for pairwise incoherence

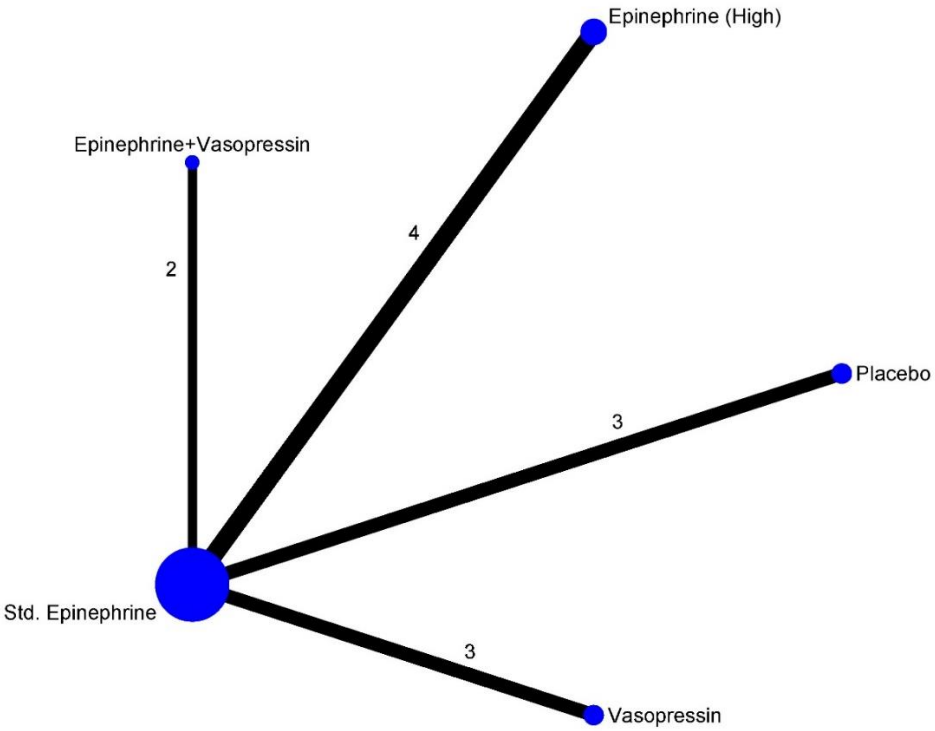
Comparison	Direct ES OR (95% CI)	I^2	Indirect ES OR (95% CI)	incoherence		P value for incoherence
				IF	SE log of IF	
Epi (high) vs Std. Epi*	0.96 (0.72, 1.29)	0.0	0.91 (0, .)	-0.119	1310.491	0.999
Epi + Vasopressin vs Std. Epi*	0.97 (0.57, 1.63)	20.6	1.01 (0, .)	0.033	978.517	0.999
Std. Epi vs Placebo*	1.07 (0.47, 2.47)	86.6	0.97 (0, .)	-0.068	356.735	0.999

Std. Epi vs Vasopressin*	0.85 (0.59, 1.20)	0.0	0.21 (0, .)	-1.273	1026.119	0.999

* All the evidence about these contrasts comes from the trials which directly compare them.

Supplemental Table 8: Network plot, Surface Under the Cumulative Ranking curve (SUCRA) and pairwise incoherence for overall survival with good functional outcome.

Network Plot



SUCRA and ranking probabilities for treatments

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	69.1	31.4	2.2
Epinephrine (High)	50.4	16.3	3
Epinephrine+Vasopressin	9.5	3.3	4.6
Epinephrine (Standard)	57.9	8.7	2.7
Vasopressin	63.1	40.3	2.5

Direct and indirect estimates of effect and P value for pairwise incoherence

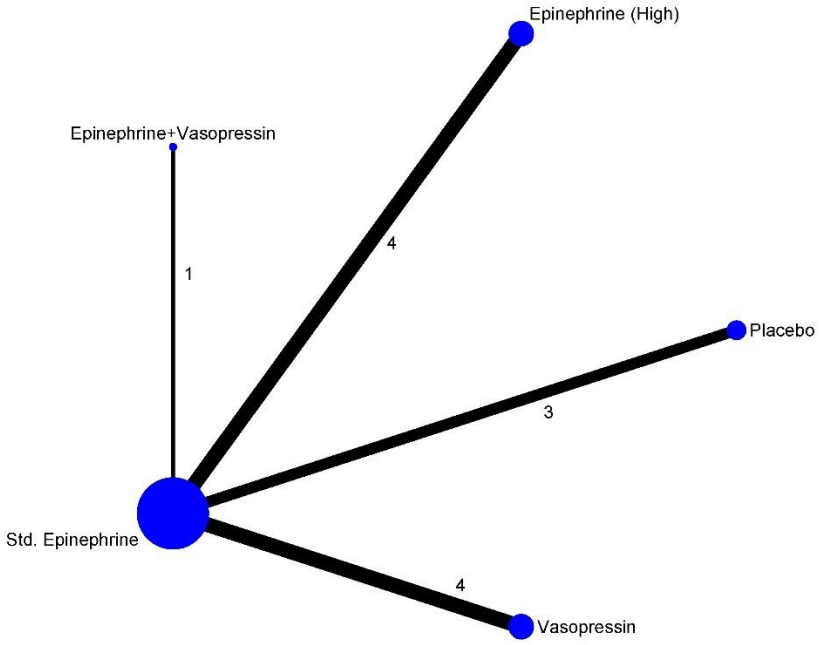
Comparison	Direct ES OR (95% CI)	I^2	Indirect ES OR (95% CI)	incoherence		P value for incoherence
				IF	SE log of IF	
Epi (high) vs Std. Epi*	0.96 (0.67, 1.36)	0.0	1.35 (0, .)	0.424	1966.549	0.999
Epi + Vasopressin vs Std. Epi*	0.58 (0.27, 1.22)	0.0	1.32 (0, .)	0.780	7033.675	0.999
Std. Epi vs Placebo*	0.87 (0.37, 2.07)	83.8	1.09 (0, .)	0.240	709.606	0.999

Std. Epi vs Vasopressin*	0.96 (0.52, 1.76)	0.0	0.86 (0, .)	-0.036	2096.445	0.999

* All the evidence about these contrasts comes from the trials which directly compare them.

Supplemental Table 9: Network plot and Surface Under the Cumulative Ranking curve (SUCRA) for **ROSC** among patients with **shockable arrest**.

Network Plot

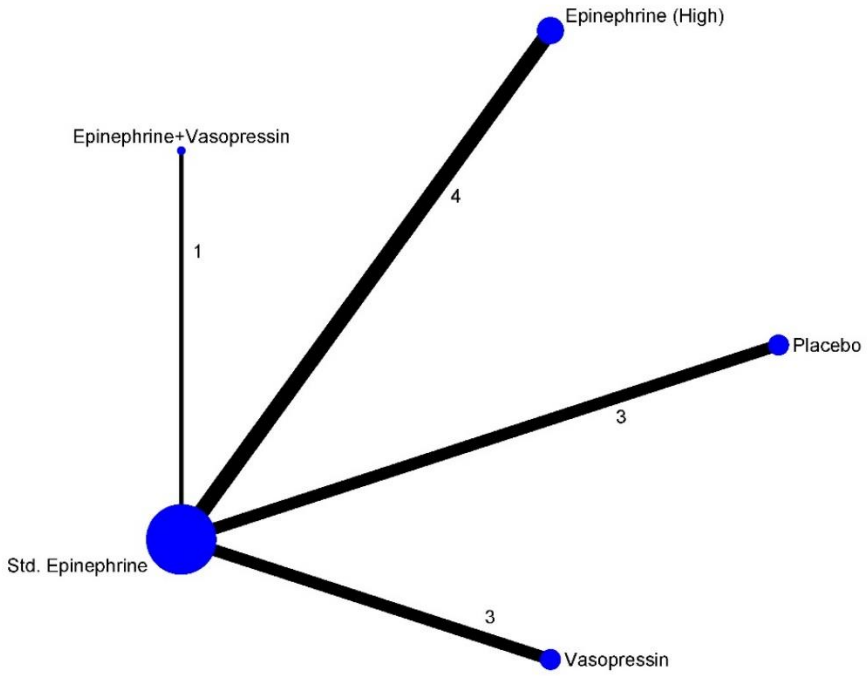


SUCRA and ranking probabilities for treatments

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	0.8	0.0	5.0
Epinephrine (High)	32.4	0.4	3.7
Epinephrine+Vasopressin	77.2	59.0	1.9
Epinephrine (Standard)	73.5	21.3	2.1
Vasopressin	66.1	19.3	2.4

Supplemental Table 10: Network plot and Surface Under the Cumulative Ranking curve (SUCRA) for **ROSC** among patients with **non-shockable arrest**.

Network Plot

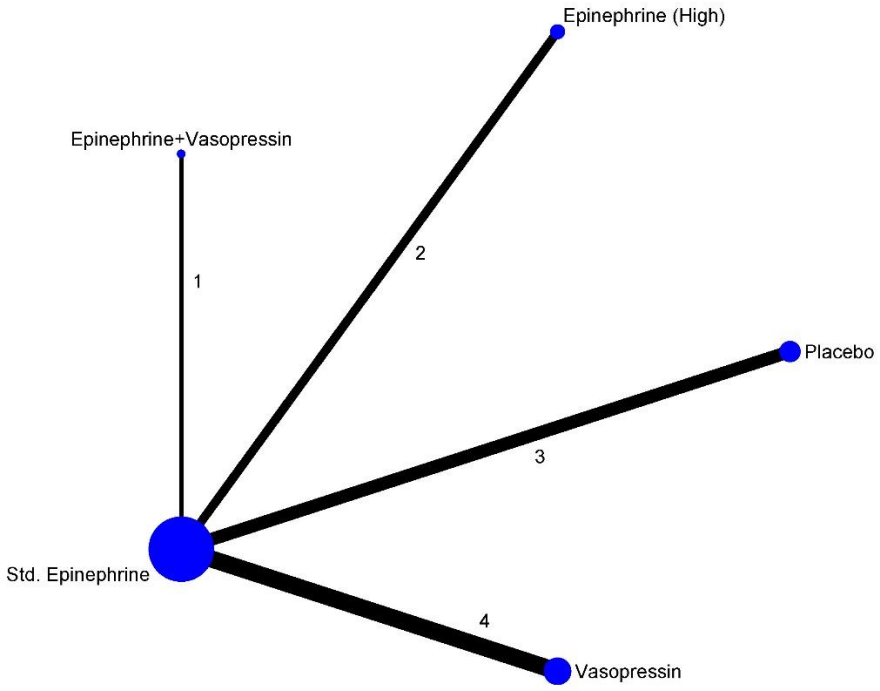


SUCRA and ranking probabilities for treatments

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	0.0	0.0	5.0
Epinephrine (High)	72.0	38.0	2.1
Epinephrine+Vasopressin	57.0	29.9	2.7
Epinephrine (Standard)	56.5	6.2	2.7
Vasopressin	64.5	25.9	2.4

Supplemental Table 11: Network plot and Surface Under the Cumulative Ranking curve (SUCRA) for **survival to admission** among patients with **shockable arrest**.

Network Plot

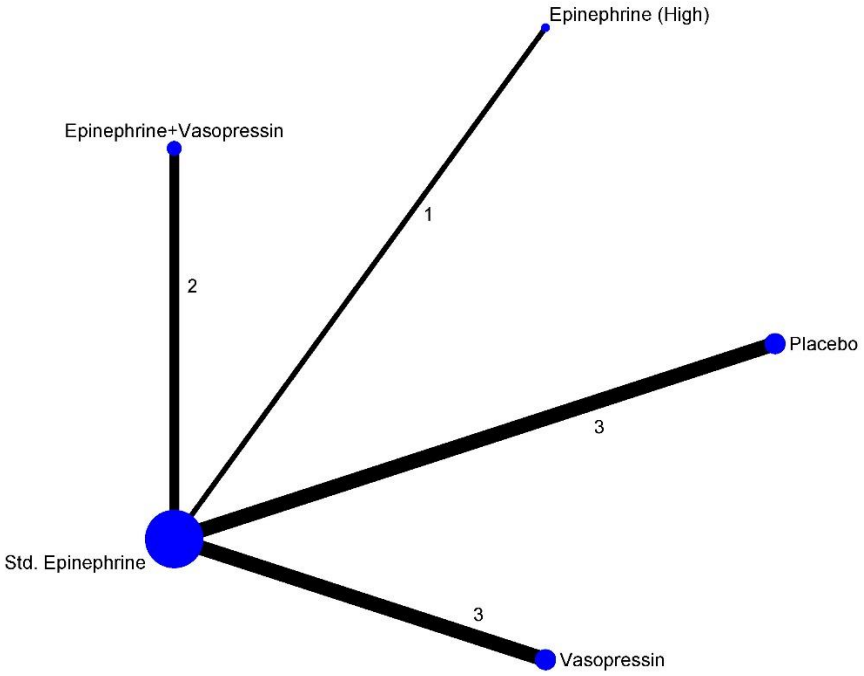


SUCRA and ranking probabilities for treatments

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	23.9	2.2	4.0
Epinephrine (High)	36.0	6.8	3.6
Epinephrine+Vasopressin	53.2	29.1	2.9
Epinephrine (Standard)	51.9	2.7	2.9
Vasopressin	85.0	59.2	1.6

Supplemental Table 12: Network plot and Surface Under the Cumulative Ranking curve (SUCRA) for **survival to admission** among patients with **non-shockable arrest**.

Network Plot

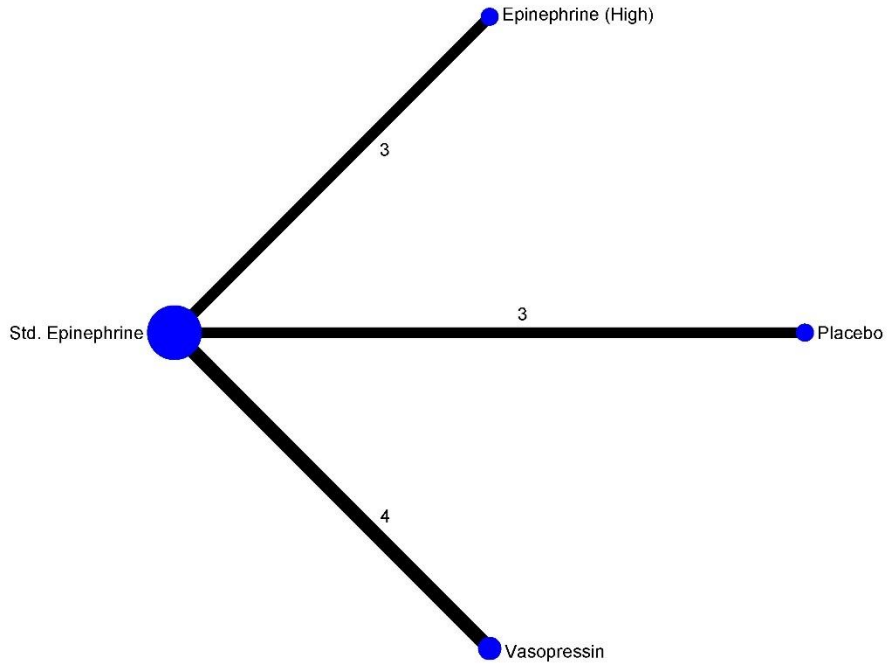


SUCRA and ranking probabilities for treatments

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	0.0	0.0	5.0
Epinephrine (High)	81.7	53.0	1.7
Epinephrine+Vasopressin	37.1	3.7	3.5
Epinephrine (Standard)	51.3	1.7	2.9
Vasopressin	80.0	41.5	1.8

Supplemental Table 13: Network plot and Surface Under the Cumulative Ranking curve (SUCRA) for **overall survival** among patients with **shockable arrest**.

Network Plot

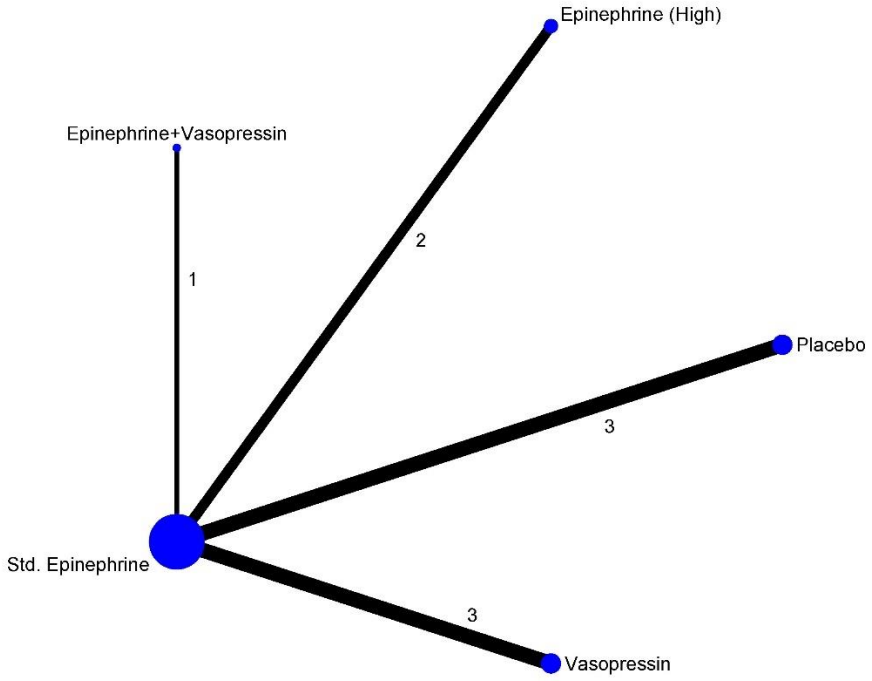


SUCRA and ranking probabilities for treatments

Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	59.3	23.2	2.2
Epinephrine (High)	10.2	1.9	3.7
Epinephrine (Standard)	44.2	3.2	2.7
Vasopressin	86.3	71.7	1.4

Supplemental Table 14: Network plot and Surface Under the Cumulative Ranking curve (SUCRA) for **overall survival** among patients with **non-shockable arrest**.

Network Plot

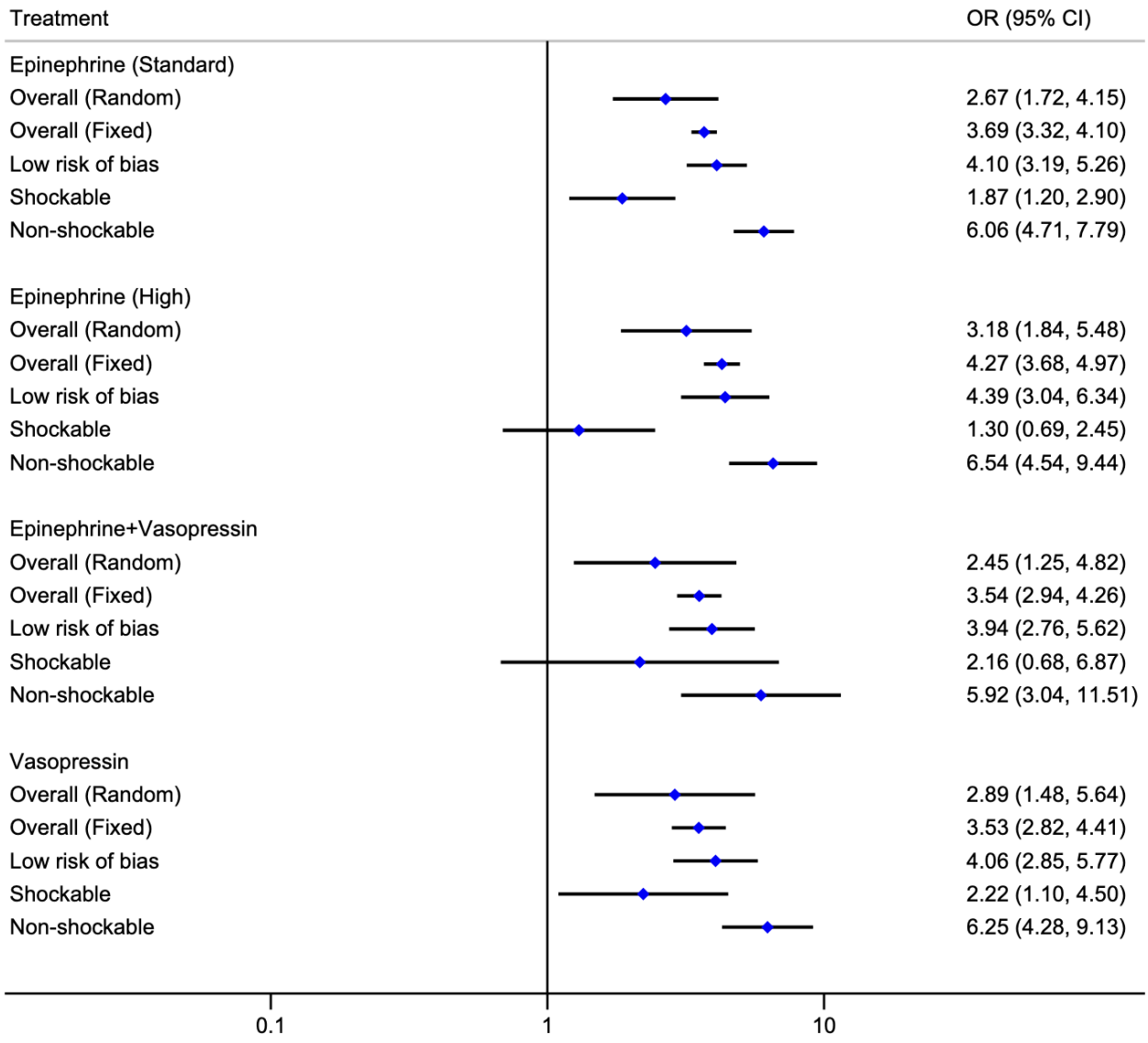


SUCRA and ranking probabilities for treatments

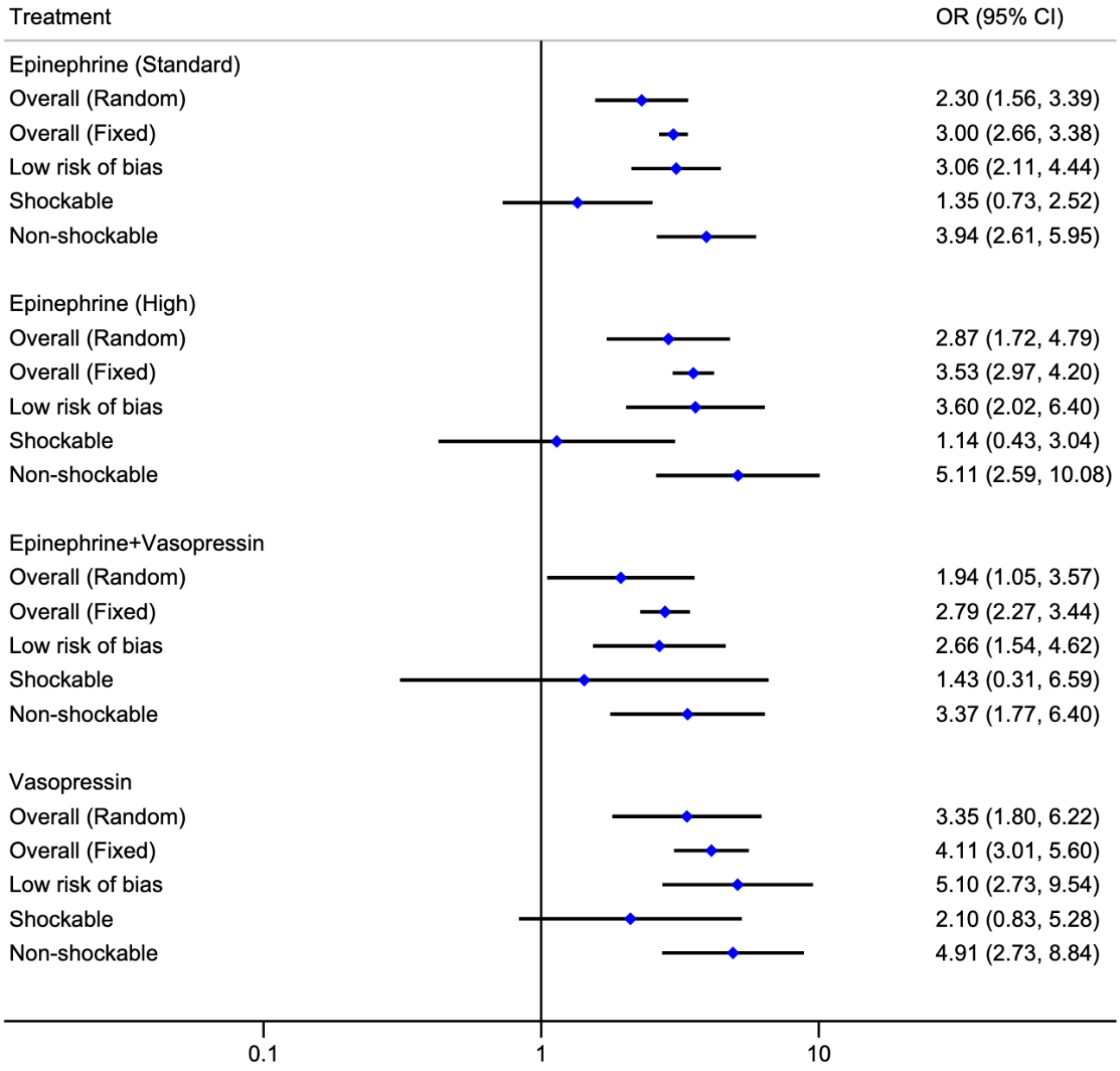
Treatment	SUCRA	Probability of being the best (%)	Mean Rank
Placebo	5.0	0.1	4.8
Epinephrine (High)	51.6	12.6	2.9
Epinephrine+Vasopressin	41.7	9.8	3.3
Epinephrine (Standard)	65.0	9.6	2.4
Vasopressin	86.7	68.0	1.5

Supplemental Figure 4: Network meta-regression results.

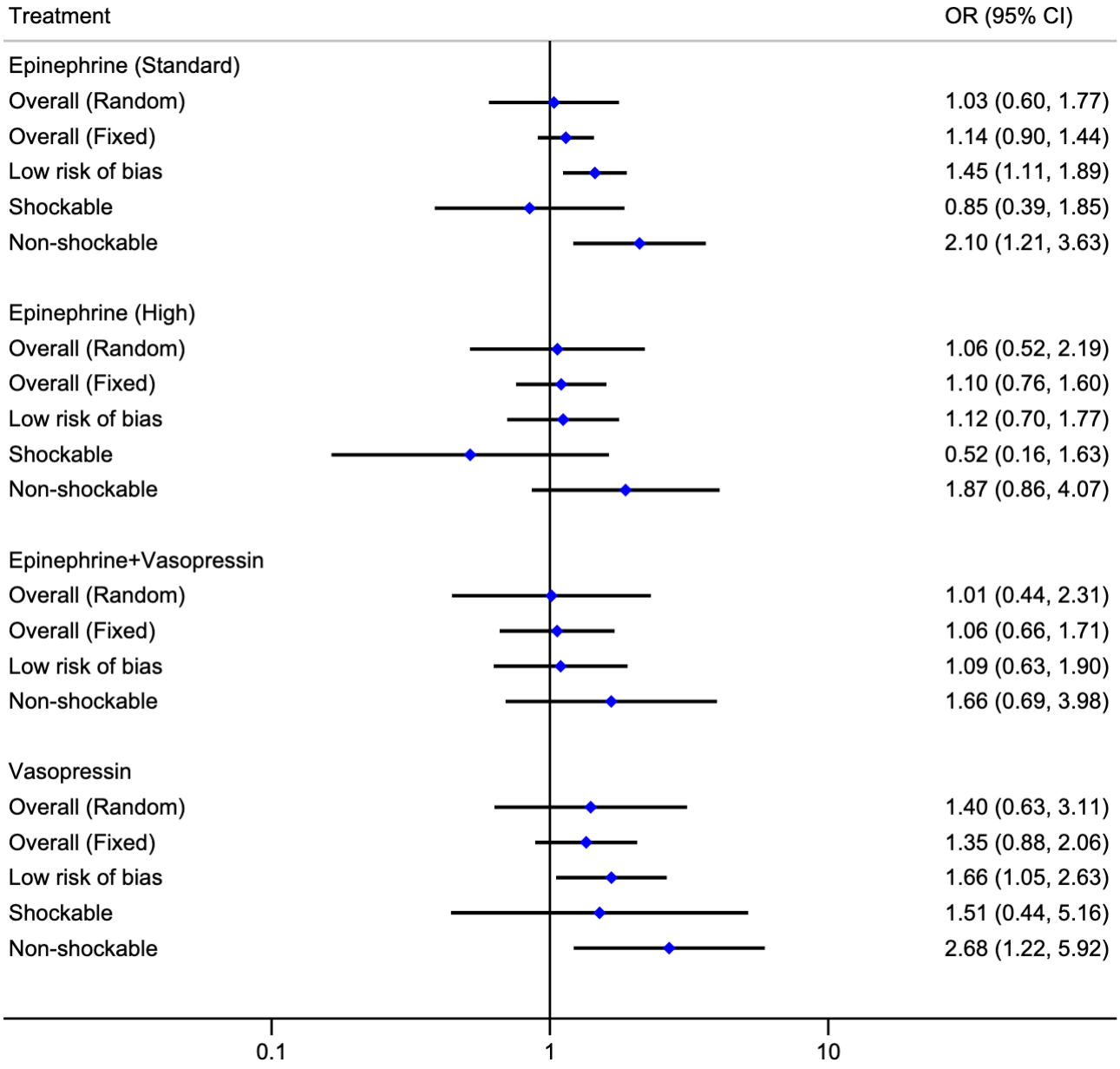
Outcome: Return of Spontaneous Circulation



Outcome: Survival to Hospital Admission



Outcome: Survival to Hospital Discharge



Outcome: Survival with Good Functional Outcome