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TITLE

Vasopressors during cardiopulmonary resuscitation. A network meta-analysis of randomized trials

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ABSTRACT

Objective: Several randomised controlled trials (RCTs) have compared adrenaline (epinephrine) with alternative therapies in patients with cardiac arrest with conflicting results. Recent observational studies suggest that adrenaline might increase return of spontaneous circulation (ROSC) but worsen neurologic outcome. We systematically compared all the vasopressors tested in RCTs in adult cardiac arrest patients in order to identify the treatment associated with the highest rate of ROSC, survival, and good neurologic outcome.

Data sources: PubMed, Embase, BioMed Central and the Cochrane Central register were searched (up to April 1st, 2017).

Study selection: We included all the RCTs comparing a vasopressor with any other therapy. A network meta-analysis with a frequentist approach was performed to identify the treatment associated with the highest likelihood of survival.

Data extraction: Two independent investigators examined and extracted data from eligible trials,

Data synthesis: Twenty-eight studies randomizing 14,848 patients in 12 treatment groups were included. Only a combined treatment with adrenaline, vasopressin and methylprednisolone was associated with increased likelihood of ROSC and survival with a good neurological outcome compared to several other comparators, including adrenaline. Adrenaline alone was not associated with any significant difference in mortality and good neurological outcome compared to any other comparators.

Conclusions: In RCTs assessing vasopressors in adults with cardiac arrest, only a combination of adrenaline, vasopressin and methylprednisolone was associated with improved survival with a good neurological outcome as compared to any other drug or placebo, particularly in in-hospital cardiac arrest. There was no significant randomized evidence to support neither discourage the use of adrenaline during cardiac arrest.

KEY WORDS

cardiac arrest; resuscitation; adrenaline; vasopressin; ROSC; survival

INTRODUCTION

Cardiac arrest is the most severe medical emergency; despite wide efforts to improve its outcome, only a minority of resuscitated patients is discharged alive in good neurological condition.

Out-of-hospital cardiac arrest (OHCA) has an estimated incidence of 55-113 cases yearly per 100,000 inhabitants with crude survival rates ranging from 6 to 22% (1-5). In-hospital cardiac arrest (IHCA) has a reported incidence of 1-5 cases every 1,000 patients (6-8), with survival rates of approximately 24% (9).

Current guidelines on cardiopulmonary resuscitation (CPR) and advanced life supports (ALS) recommend the administration of 1 mg of adrenaline (epinephrine) via intra-venous or intra-osseous route every 3-5 minutes during resuscitation; however, this recommendation is based on expert opinion and there is no direct evidence that adrenaline increases survival to hospital discharge (10). In addition, recent observational studies suggest that administration of adrenaline may increase the rate of return of spontaneous circulation (ROSC) but at the cost of a worse neurologic outcome in survivors (17).

Several randomised controlled trials (RCTs) have compared standard adrenaline with higher doses of adrenaline, alternative vasopressors (e.g. vasopressin), combinations of vasopressors, or placebo (11-16), with conflicting results. However, results of these trials have not been compared each other in order to detect which pharmacological strategy is the best (18).

A network meta-analysis is a statistical technique that allows performing an indirect comparison between treatments that have never been directly compared in randomised clinical trials (19-21). Therefore, we performed a network meta-analysis to indirectly compare and grade all the vasopressor drugs tested in RCTs in adult patients with cardiac arrest in order to identify the treatment associated with the highest survival rate, the highest likelihood of ROSC, and the best neurological outcome.

MATERIALS AND METHODS

We performed a systematic review and network meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (PRISMA-NMA Checklist available as Supplemental Digital Content) (22-25).

Data Sources and Search Strategy

Relevant studies were searched on PubMed, Embase, BioMed Central and the Cochrane Central register by two independent investigators. Our search strategy aimed to include every RCT investigating the use of a vasopressor agent in adult patients with cardiac arrest. In addition, we employed backward snowballing (i.e., scanning of references of retrieved articles and pertinent reviews) to identify further studies. Literature search was last updated April 1st, 2017. The PubMed search strategy, modified from Biondi-Zoccai et al (26), is available in the Supplemental Digital Content.

Study Selection

Two investigators first examined references at a title/abstract level, and then, if potentially pertinent, retrieved the complete articles. All RCTs on adult patients in cardiac arrest, with at least one group randomised to receive a vasopressor and published as full text, were considered for inclusion. Exclusion criteria were non-adult population, overlapping population, lack of mortality data, study published as abstract only, and study investigating drugs not available on the market.

Data Extraction and Quality Assessment

Cardiac arrest setting, presentation rhythm, procedural, outcome and follow-up data were independently abstracted by two investigators. Patients randomised to placebo and those randomised to standard treatment were aggregated together as a single comparison group. Two independent investigators assessed the internal validity and risk of bias (at a study level) of included

trials according to the “Risk of bias assessment tool” developed by The Cochrane collaboration (27). Disagreements between assessors were resolved by consensus.

Data Synthesis and Analysis

Primary outcome was survival at the longest follow-up available, while secondary outcomes were ROSC rate, and survival with a good neurological outcome at the longest follow-up available. Good neurological outcome was defined according as per Authors’ definition in each study (detailed in Supplementary Table 4). Subgroup analyses included patients with IHCA versus OHCA, and patients with shockable versus non-shockable presentation rhythms.

Dichotomous variables were reported as percentages while continuous variables were reported as mean ± standard deviation or median (interquartile range). Network meta-analysis with a frequentist approach was used to compare mortality at the longest follow-up available between different therapies using the netmeta R package version 8.0 (available at: http://CRAN.R-project.org/package=netmeta) to calculate point estimates of risk differences (RD) with 95% confidence intervals (CI) and generate head-to-head comparison and forest plots using fixed-effects (in case of low heterogeneity/inconsistency), and random-effects models (in case of high heterogeneity/inconsistency) comparing the effect estimates of different therapies relative to LD-adrenaline (21). P rank scores were generated to determine probability scores to rank which therapies result in the highest survival. Heterogeneity and inconsistency were assessed to generate heat plots, these are a matrix visualization proposed by Krahn and colleagues (28) that highlight hot spots of inconsistency between specific direct evidence in the whole network and allows to highlight possible drivers. Data were analysed according to the intention-to-treat principle whenever possible. Statistical analysis was performed using R (29), with statistical significance for hypothesis testing set at the 0.05 two-tailed level and for heterogeneity testing at the 0.10 two-tailed level.

RESULTS

Study characteristics

The literature search yielded a total of 372 studies. A total of 19 studies were excluded due to pre-specified criteria. The complete list of excluded studies, along with reasons for their exclusion, is presented in Supplementary Table 1. Finally, 28 studies randomizing 14,848 patients in 12 treatment groups (comparators) were included in the final analysis (Figure 1) (11-16, 30-51). The characteristics of included trials are described in Tables 1 and 2.

Twenty-six of 28 the included studies randomised patients into two treatment groups, while two studies randomised patients into three treatment groups (31,34). Thereby, a total of 58 treatment arms were analysed. The most frequently investigated comparators were low-dose adrenaline (7,211 patients in 26 treatment arms), high-dose adrenaline (3,328 patients in 10 treatment arms), a combination of adrenaline plus vasopressin (1,673 patients in 4 treatment arms), and a combination treatment of adrenaline, vasopressin and methylprednisolone (206 patients in 2 treatment arms). Network configuration is presented in Figure 2.

Seven studies were judged to be at low risk of bias (11, 15, 32, 38, 40, 41, 47), 10 studies at unclear risk of bias (12, 13, 16, 34, 39, 43-45, 48, 49), and 11 studies at high risk of bias (14, 30,31,33, 35-37, 42, 46, 50, 51) (Supplementary Table 2).

Quantitative Data Synthesis

Overall survival

Among the 12 treatments analysed, the combination of adrenaline, vasopressin and methylprednisolone (15, 41) was associated with increased likelihood of survival as compared with low-dose adrenaline (RD vs. LD-adrenaline = 0.06, 95% CI = 0.01 to 0.11) (Table 3). Rank analysis showed that this combination had the highest probability to be the best treatment in terms of survival, followed by noradrenaline (norepinephrine), vasopressin, phenylephrine and LD-adrenaline (Table 3).

Network head-to-head comparison showed that the combination of adrenaline, vasopressin and methylprednisolone (15, 41) was associated with an increased survival when compared also to HD-adrenaline, vasopressin, the combination of adrenaline-vasopressin, methoxamine, and placebo (Supplementary Table 3). Heterogeneity among studies was low (I^2 = 0%, Q statistics p-value = 0.50).

ROSC

Rank analysis showed that adrenaline-vasopressin-methylprednisolone had the highest probability to be the best pharmacological treatment, followed by noradrenaline and HD-adrenaline, phenylephrine, and vasopressin.

Head-to-head comparison showed an increased probability of ROSC with adrenaline-vasopressin-methylprednisolone compared to HD-adrenaline, vasopressin, adrenaline-vasopressin, methoxamine, and placebo. Conversely, methoxamine reduced ROSC probability compared with HD-adrenaline, vasopressin, and noradrenaline (Supplementary Tables 4 and 10). Heterogeneity among studies was high (I^2 = 61.4%, Q statistics p-value = 0.0003).

Good neurological outcome

Using LD-adrenaline as reference, only the combination of adrenaline, vasopressin and methylprednisolone was associated with increased survival with a good neurological outcome (RD vs LD-adrenaline = 0.06, 95% CI = 0.01 to 0.10). Head-to-head network comparison showed increased survival with good neurological outcome when adrenaline-vasopressin-methylprednisolone was compared with HD-adrenaline, vasopressin, adrenaline-vasopressin, noradrenaline, and placebo (Supplementary Tables 5 and 11). Heterogeneity among studies was low (I^2 = 0%, Q statistics p-value = 0.69).

In- and out-of-hospital cardiac arrest

When analysing studies investigating OHCA, no treatment was associated with increased survival compared to others (Supplementary Tables 8 and 14). Heterogeneity among studies was low (I^2 = 0%, Q statistics p-value = 0.50).

Considering IHCA, the combination of adrenaline, vasopressin and methylprednisolone was associated with increased survival as compared to LD-adrenaline (RD = 0.06, 95% CI = 0.01 to 0.11). Head-to-head comparison showed increased survival associated with adrenaline-vasopressin-methylprednisolone treatment when compared to HD-adrenaline (RD = 0.07, 95% CI = 0.01 to 0.14) (Supplementary Tables 9 and 15). Heterogeneity among studies was moderate (I^2 = 30.5%, Q statistics p-value = 0.23).

Outcomes according to initial rhythm

When analysing treatments for cardiac arrest with an initial shockable rhythm, we found that no treatment was superior to another in terms of survival. Heterogeneity among studies was low (I^2 = 12.8%, Q statistics p-value = 0.33) (Supplementary Tables 5 and 11).

Similarly, no treatment was associated with increased survival when analysing data on cardiac arrest with a non-shockable rhythm at presentation (Supplementary Tables 7 and 13). Heterogeneity among studies was low (I^2 = 0%, Q statistics p-value = 0.60).

DISCUSSION

In this large network meta-analysis of randomised trials investigating vasopressors during CPR, we found that only a combined treatment with adrenaline, vasopressin and methylprednisolone (15, 41) was associated with a significantly higher likelihood of ROSC, survival, and good neurological outcome compared to LD-adrenaline and to several other comparators. Conversely, methoxamine, an α_1-adrenergic agonist (52), was associated with reduced likelihood of ROSC. Considering IHCA, the combined treatment with adrenaline, vasopressin and methylprednisolone was once again the

only treatment associated with increased survival; on the other hand, in OHCA no treatment was found to be superior over the others.

Compared to previous systematic reviews and meta-analyses published on the topic (53-58), this is the first study to compare and grade using a statistical analysis the efficacy of all vasopressors tested during CPR in RCTs. In contrast, previous meta-analyses focused on single agents, usually adrenaline (54, 56, 57) or vasopressin (55, 58). The most comprehensive systematic (but not quantitative) review published so far by Larabee and colleagues in 2012 included all agents included in our study, and concluded that adrenaline (both a standard dose and at high dose) provide a short-term benefit in terms of ROSC, that there are insufficient evidences to support or discourage vasopressin use, and that noradrenaline may provide superior results in terms of ROSC as compared with adrenaline (53). A major difference with our study is that Larabee and colleagues did not perform a statistical analysis of their results.

The most widely investigated alternative to adrenaline has been vasopressin. Current evidence concerning vasopressin use in cardiac arrest showed no survival benefit in unselected patient population. A meta-analysis by Mentzelopoulos and colleagues published in 2012 showed that vasopressin vs. control was associated with higher long-term survival only in patients with asystole, especially when the drug was administered within 20 minutes from arrest (58). In 2014, a meta-analysis from Layek and colleagues showed, only in subgroup analysis, that vasopressin was associated with an increased likelihood of ROSC when the drug was used in the setting of IHCA, and an increased likelihood of survival to hospital discharge and survival with a favourable neurological outcome when vasopressin was administered as “repeated boluses of 4–5 times titrated to the desired effects” (55). However, in the meta-analyses above the results of the combination of vasopressin, steroids and adrenaline was pooled together with vasopressin. We found no significant increase in the rate of ROSC or survival to the longest follow-up available when vasopressin was used as compared to other agents. The most likely explanation for these different findings is that results of the meta-analysis by Layek and colleagues are significantly influenced by the two studies

performed by Mentzelopoulos and colleagues (15,41), which were analysed together with studies on vasopressin. In contrast, in our study we grouped these two RCTs separately since the administration of vasopressin was combined to adrenaline and methylprednisolone, and the study design included also a post-resuscitation treatment.

In their meta-analysis of RCTs and observational trials on adrenaline use during cardiopulmonary resuscitation Patanwala and colleagues found that adrenaline was associated with decreased survival after cardiac arrest. However, their analysis included observational studies, subjected to higher risk of bias than RCTs, that mainly influenced the results (56). Differently from that study, we included only RCTs.

In our study we were able to identify a treatment that, compared to all other vasopressors administered during CPR ever tested in RCTs, was shown to increase survival with a good neurological outcome. Differently from previous literature, our results are for the first time supported by a statistical approach indirectly comparing the efficacy of all treatments ever assessed in RCTs. However, we acknowledge that these results are mainly driven by two studies by Mentzelopoulos et al., which were performed in the setting of IHCA, with a relevant proportion of patients being already in an intensive care unit (15), where all equipment for ALS and post-resuscitation care are readily available, and the staff is well trained in the management of cardiac arrest. Another possible explanation for the positive results obtained by Mentzelopoulos and colleagues is the effect of steroids on post-resuscitation syndrome. Steroids administration could attenuate post-arrest systemic inflammatory response syndrome (59,60). In addition, release of adrenal hormone is frequently impaired after cardiac arrest, which reduces the physiological stress response (61,62). Finally, steroids may increase response to vasopressors due to their effect on intracellular signalling pathways (63).

Current ALS guidelines recommend administration of 1 mg adrenaline during CPR (10). This recommendation is based on low quality of evidence, in particular on old, nonrandomised trials, and has been part of resuscitation guidelines for decades (64). Although in our trial we found that only

epinephrine-vasopressin-methylprednisolone combination was associated with increased survival, results of ranking analysis provide some interesting clues. Standard dose adrenaline was ranked only fifth, behind epinephrine-vasopressin-methylprednisolone, norepinephrine, and phenylephrine, while the combination adrenaline-vasopressin, was ranked only tenth. This suggests that the two most widely used and investigated vasopressors or combination of vasopressors may not necessarily be the most effective in terms of potential impact on survival.

Interestingly, adrenaline (a potent β- and α-adrenergic agonist) was ranked below noradrenaline (which has higher affinity for α-adrenergic receptors than for β-receptors) and phenylephrine (a pure α-adrenergic agonist). Currently, several nonrandomised studies have questioned the benefit of adrenaline administration during CPR, as they showed worse neurological outcome in patients receiving adrenaline, even in the face of an increased incidence in ROSC (17, 65-68). In our study, we found no evidence of worse outcome associated with either high or low dose adrenaline. However, it should be noted that most of the studies compared adrenaline with another vasopressor, and use of open-label, standard dose adrenaline was generally allowed at some point of CPR algorithm in most of the studies. An ongoing randomised trial will hopefully provide a definitive answer on the role of pre-hospital adrenaline administration (PARAMEDIC-2 [ISRCTN73485024]) (76). multicentre before use

A strength of our study is that we systematically searched and included only RCTs performed on this topic. In contrast to previous reviews and meta-analyses, our network meta-analytic statistical approach allowed us to indirectly compare all the vasopressors used in RCT among each other.

Our study has some limitations. Firstly, we included studies performed in both OHCA and IHCA settings. However, we performed specific subgroup analyses for the different settings showing that the positive results of a combined treatment of vasopressin, adrenaline, and methylprednisolone arise from two studies performed by Mentzelopoulos et al. in IHCA. Secondly, the quality of included trials was heterogeneous, with the majority of trials carrying a unclear or a high risk of bias. Finally, all limitations of meta-analyses apply also to network meta-analyses (20,23). In

particular, meta-analyses should be considered hypothesis generating, particularly when available trials are heterogeneous or with high risk of bias.

CONCLUSIONS

This network meta-analysis of RCTs found that only a combined treatment with adrenaline, vasopressin and methylprednisolone was associated with improved survival with a good neurological outcome and ROSC probability compared to several other comparators, including adrenaline, particularly in IHCA. No significant randomised evidences support neither discourage the use of adrenaline during cardiac arrest. High-quality studies are needed to confirm these findings and explore further therapeutic treatments in this setting.

CONFLICT OF INTEREST

None

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REFERENCES

1. Perkins GD, Handley AJ, Koster RW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 2. Adult basic life support and automated external defibrillation. *Resuscitation* 2015;95:81-99.

2. Berdowski J, Berg RA, Tijssen JG, et al. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. *Resuscitation* 2010;81:1479-1487.

3. Gräsner JT, Herlitz J, Koster RW, et al. Quality management in resuscitation--towards a European cardiac arrest registry (EuReCa). *Resuscitation* 2011;82:989-994.

4. Gräsner JT, Bossaert L. Epidemiology and management of cardiac arrest: what registries are revealing. *Best Pract Res Clin Anaesthesiol* 2013;27:293-306.

5. Hawkes C, Booth S, Ji C, et al. Epidemiology and outcomes from out-of-hospital cardiac arrests in England. Resuscitation. *Resuscitation* 2017;110:133-140.

6. Hodgetts TJ, Kenward G, Vlackonikolis I, et al. Incidence, location and reasons for avoidable in-hospital cardiac arrest in a district general hospital. *Resuscitation* 2002;54:115-123.

7. Skogvoll E, Isern E, Sangolt GK, et al. In-hospital cardiopulmonary resuscitation. 5 years' incidence and survival according to the Utstein template. *Acta Anaesthesiol Scand* 1999;43:177-184.

8. Sandroni C, Ferro G, Santangelo S, et al. In-hospital cardiac arrest: survival depends mainly on the effectiveness of the emergency response. *Resuscitation* 2004;62:291-297.

9. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation* 2016;133:e38-e360.

10. Soar J, Nolan JP, Böttiger BW, et al. European Resuscitation Council Guidelines for Resuscitation 2015: Section 3. Adult advanced life support. *Resuscitation* 2015;95:100-147.

11. Wenzel V, Krismer AC, Arntz HR, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004;350:105-113.

12. Gueugniaud PY, Mols P, Goldstein P, et al. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. European Epinephrine Study Group. *N Engl J Med* 1998;339:1595-1601.

13. Gueugniaud PY, David JS, Chanzy E, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med* 2008;359:21-30.

14. Patrick WD, Freedman J, McEwen T, et al. A randomized, double-blind comparison of methoxamine and epinephrine in human cardiopulmonary arrest. *Am J Respir Crit Care Med* 1995;152:519-523.

15. Mentzelopoulos SD, Malachias S, Chamos C, et al. Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial. *JAMA* 2013;310:270-279.

16. Jacobs IG, Finn JC, Jelinek GA, et al. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. *Resuscitation* 2011;82:1138-1143.

17. Loomba RS, Nijhawan K, Aggarwal S, et al. Increased return of spontaneous circulation at the expense of neurologic outcomes: Is prehospital epinephrine for out-of-hospital cardiac arrest really worth it? *J Crit Care* 2015;30:1376-1381.

18. Baker SG, Kramer BS. The transitive fallacy for randomized trials: if A bests B and B bests C in separate trials, is A better than C? *BMC Med Res Methodol* 2002;2:13

19. Song F, Altman DG, Glenny AM, et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. *BMJ* 2003;326:472.

20. Greco T, Biondi-Zoccai G, Saleh O, et al. The attractiveness of network meta-analysis: a comprehensive systematic and narrative review. *Heart Lung Vessel* 2015;7:133-142.

21. Biondi-Zoccai G (Eds): Network Meta-Analysis: Evidence Synthesis with Mixed Treatment Comparison. Hauppauge (NY), Nova Science Publishers, 2014.

22. Biondi-Zoccai G, Lotrionte M, Landoni G, et al. The rough guide to systematic reviews and meta-analyses. *HSR Proc Intensive Care Cardiovasc Anesth* 2011;3:161-173.

23. Greco T, Zangrillo A, Biondi-Zoccai G, et al. Meta-analysis: pitfalls and hints. *Heart Lung Vessel* 2013;5:219-225.

24. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med* 2009;6:e1000100.

25. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777-784.

26. Biondi-Zoccai GG, Agostoni P, Abbate A, et al. A simple hint to improve Robinson and Dickersin's highly sensitive PubMed search strategy for controlled clinical trials. *Int J Epidemiol* 2005;34:224-225.

27. Higgins J, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.

28. Krahn U, Binder H, König J. A graphical tool for locating inconsistency in network meta-analyses. *BMC Med Res Methodol* 2013;13:35.

29. The R Core Team. R: A Language and Environment for Statistical Computing. Version 3.3.2. Available at: https://cran.r-project.org/doc/manuals/r-release/fullrefman.pdf. Accessed November 15th, 2016.

30. Brown CG, Martin DR, Pepe PE, et al. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. The Multicenter High-Dose Epinephrine Study Group. *N Engl J Med* 1992;327:1051-1055.

31. Callaham M, Madsen CD, Barton CW, et al. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. *JAMA* 1992;268:2667-2672.

32. Callaway CW, Hostler D, Doshi AA, et al. Usefulness of vasopressin administered with epinephrine during out-of-hospital cardiac arrest. *Am J Cardiol* 2006;98:1316-1321.

33. Choux C, Gueugniaud PY, Barbieux A, et al. Standard doses versus repeated high doses of epinephrine in cardiac arrest outside the hospital. *Resuscitation* 1995;29:3-9.

34. Ducros L, Vicaut E, Soleil C, et al. Effect of the addition of vasopressin or vasopressin plus nitroglycerin to epinephrine on arterial blood pressure during cardiopulmonary resuscitation in humans. *J Emerg Med* 2011;41:453-459.

35. Ghafourian N, Maniae NH, Taherikalani M, et al. Combination of Vasopressin-Epinephrine as a Novel Candidate in Patients with Cardiac Arrest. *Recent Adv Cardiovasc Drug Discov* 2015;10:65-69.

36. Jaffe R, Rubinshtein R, Feigenberg Z, et al. Evaluation of isoproterenol in patients undergoing resuscitation for out-of-hospital asystolic cardiac arrest (the Israel Resuscitation with Isoproterenol Study Prospective Randomized Clinical Trial). *Am J Cardiol* 2004;93:1407-9, A9.

37. Lindner KH, Ahnefeld FW, Grünert A. Epinephrine versus norepinephrine in prehospital ventricular fibrillation. *Am J Cardiol* 1991;67:427-428.

38. Lindner KH, Dirks B, Strohmenger HU, et al. Randomised comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet* 1997;349:535-537.

39. Lindner KH, Ahnefeld FW, Prengel AW. Comparison of standard and high-dose adrenaline in the resuscitation of asystole and electromechanical dissociation. *Acta Anaesthesiol Scand* 1991;35:253-256.

40. Lipman J, Wilson W, Kobilski S, et al. High-dose adrenaline in adult in-hospital asystolic cardiopulmonary resuscitation: a double-blind randomised trial. *Anaesth Intensive Care* 1993;21:192-196.

41. Mentzelopoulos SD, Zakynthinos SG, Tzoufi M, et al. Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest. *Arch Intern Med* 2009;169:15-24.

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

43. Olson DW, Thakur R, Stueven HA, et al. Randomized study of epinephrine versus methoxamine in prehospital ventricular fibrillation. *Ann Emerg Med* 1989;18:250-253.

44. Ong ME, Tiah L, Leong BS, et al. A randomised, double-blind, multi-centre trial comparing vasopressin and adrenaline in patients with cardiac arrest presenting to or in the Emergency Department. *Resuscitation* 2012;83:953-960.

45. Sherman BW, Munger MA, Foulke GE, et al. High-dose versus standard-dose epinephrine treatment of cardiac arrest after failure of standard therapy. *Pharmacotherapy* 1997;17:242-247.

46. Silfvast T, Saarnivaara L, Kinnunen A, et al. Comparison of adrenaline and phenylephrine in out-of-hospital cardiopulmonary resuscitation. A double-blind study. *Acta Anaesthesiol Scand* 1985;29:610-613.

47. Stiell IG, Hébert PC, Wells GA, et al. Vasopressin versus epinephrine for inhospital cardiac arrest: a randomised controlled trial. *Lancet* 2001;358:105-109.

48. Stiell IG, Hebert PC, Weitzman BN, et al. High-dose epinephrine in adult cardiac arrest. *N Engl J Med* 1992;327:1045-1050.

49. Turner LM, Parsons M, Luetkemeyer RC, et al. A comparison of epinephrine and methoxamine for resuscitation from electromechanical dissociation in human beings. *Ann Emerg Med* 1988;17:443-449.

50. Weaver WD, Fahrenbruch CE, Johnson DD, et al. Effect of epinephrine and lidocaine therapy on outcome after cardiac arrest due to ventricular fibrillation. *Circulation* 1990;82:2027-2034.

51. Woodhouse SP, Cox S, Boyd P, et al. High dose and standard dose adrenaline do not alter survival, compared with placebo, in cardiac arrest. *Resuscitation* 1995;30:243-249.

52. Pazdernik TL, Kerecsen L: Rapid Review Pharmacology. 2nd ed. Philadelphia(PA), Mosby-Elsevier, 2007:39.

53. Larabee TM, Liu KY, Campbell JA, et al. Vasopressors in cardiac arrest: a systematic review. *Resuscitation* 2012;83:932-939.

54. Atiksawedparit P, Rattanasiri S, McEvoy M, et al. Effects of prehospital adrenaline administration on out-of-hospital cardiac arrest outcomes: a systematic review and meta-analysis. *Crit Care* 2014;18:463.

55. Layek A, Maitra S, Pal S, et al. Efficacy of vasopressin during cardio-pulmonary resuscitation in adult patients: a meta-analysis. *Resuscitation* 2014;85:855-863.

56. Patanwala AE, Slack MK, Martin JR, et al. Effect of epinephrine on survival after cardiac arrest: a systematic review and meta-analysis. *Minerva Anestesiol* 2014;80:831-843.

57. Lin S, Callaway CW, Shah PS, et al. Adrenaline for out-of-hospital cardiac arrest resuscitation: a systematic review and meta-analysis of randomized controlled trials. *Resuscitation* 2014;85:732-740.

58. Mentzelopoulos SD, Zakynthinos SG, Siempos I, et al. Vasopressin for cardiac arrest: meta-analysis of randomized controlled trials. *Resuscitation* 2012;83:32-39.

59. Schneider A, Albertsmeier M, Böttiger BW, et al. [Post-resuscitation syndrome. Role of inflammation after cardiac arrest]. *Anaesthesist* 2012;61:424-436.

60. Adrie C, Laurent I, Monchi M, et al. Postresuscitation disease after cardiac arrest: a sepsis-like syndrome? *Curr Opin Crit Care* 2004;10:208-212.

61. Hékimian G, Baugnon T, Thuong M, et al. Cortisol levels and adrenal reserve after successful cardiac arrest resuscitation. Shock 2004;22:116-119.

62. Pene F, Hyvernat H, Mallet V, et al. Prognostic value of relative adrenal insufficiency after out-of-hospital cardiac arrest. *Intensive Care Med* 2005;31:627-633.

63. Buddineni JP, Callaway C, Huang DT. Epinephrine, vasopressin and steroids for in-hospital cardiac arrest: the right cocktail therapy? *Crit Care* 2014;18:308.

64. Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). 3. Advanced life support. *JAMA* 1974;227:Suppl:852-860.

65. Hagihara A, Hasegawa M, Abe T, et al. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. *JAMA* 2012;307:1161-1168.

66. Olasveengen TM, Wik L, Sunde K, et al. Outcome when adrenaline (epinephrine) was actually given vs. not given - post hoc analysis of a randomized clinical trial. *Resuscitation* 2012;83:327-332.

67. Andersen LW, Kurth T, Chase M, et al. Early administration of epinephrine (adrenaline) in patients with cardiac arrest with initial shockable rhythm in hospital: propensity score matched analysis. *BMJ* 2016;353:i1577.

68. Dumas F, Bougouin W, Geri G, et al. Is epinephrine during cardiac arrest associated with worse outcomes in resuscitated patients? *J Am Coll Cardiol* 2014;64:2360-2367.

69. Perkins GD, Quinn T, Deakin CD, et al. Pre-hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug administration In Cardiac arrest (PARAMEDIC-2): Trial protocol. *Resuscitation* 2016;108:75-81.

FIGURE LEGENDS

Figure 1. Flow-chart for included studies. CPR: cardiopulmonary resuscitation

Figure 2. Network configuration. Adr: adrenaline; AVM: adrenaline + vasopressin + methylprednisolone; HD: high-dose; Iso: isoproterenol; LD: low-dose; Lido: lidocaine; Mtx: methoxamine; Nor: noradrenaline; Ntg: mitroglycerin; Phe: phenylephrine; Plac: placebo; Vas: vasopressin