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Review

Vasopressin and glucocorticoids for in-hospital cardiac arrest: A systematic review and meta-analysis of individual participant data

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Abstract

Aim: To perform a systematic review and individual participant data meta-analysis of vasopressin and glucocorticoids for the treatment of cardiac arrest.

Methods: The PRISMA-IPD guidelines were followed. We searched Medline, Embase, and the Cochrane Library for randomized trials comparing vasopressin and glucocorticoids to placebo during cardiac arrest. The population included adults with cardiac arrest in any setting. Pairs of investigators reviewed studies for relevance, extracted data, and assessed risk of bias. Meta-analyses were conducted using individual participant data. A Bayesian framework was used to estimate posterior treatment eects assuming various prior beliefs. The certainty of evidence was evaluated using GRADE.

Results: Three trials were identified including adult in-hospital cardiac arrests only. Individual participant data were obtained from all trials yielding a total of 869 patients. There was some heterogeneity in post-cardiac arrest interventions between the trials. The results favored vasopressin and glucocorticoids for return of spontaneous circulation (odds ratio: 2.09, 95%CI: 1.54 to 2.84, moderate certainty). Estimates for survival at discharge (odds ratio: 1.39, 95%CI: 0.90 to 2.14, low certainty) and favorable neurological outcome (odds ratio: 1.64, 95%CI, 0.99 to 2.72, low certainty) were more uncertain. The Bayesian estimates for return of spontaneous circulation were consistent with the primary analyses, whereas the estimates for survival at discharge and favorable neurological outcome were more dependent on the prior belief.

Conclusions: Among adults with in-hospital cardiac arrest, vasopressin and glucocorticoids compared to placebo, improved return of spontaneous circulation. Larger trials are needed to determine whether there is an eect on longer-term outcomes.

Keywords: Cardiac arrest, Glucocorticoids, Steroids, Vasopressin, Individual participant data, Meta-analysis

Introduction

Despite advancement in the management of cardiac arrest over the past decades, outcomes remain dismal.[1–3] The treatment of cardiac arrest includes basic life support (e.g., chest compressions and ventilations), advanced life support (e.g., defibrillation and drugs), and post-cardiac arrest care.[4,5] However, there is limited evidence to support many of the advanced therapies currently used during cardiac arrest and there is an unmet need for new pharmacological interventions to improve patient outcomes.[6] For example, the effect of epinephrine and amiodarone, which are the only two drugs

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recommended for routine use in cardiac arrest, is uncertain for long-term outcomes and studies have mainly been conducted in the out-of-hospital setting.

Vasopressin has been proposed as beneficial during cardiac arrest as vasoconstriction may increase coronary perfusion pressure and result in return of spontaneous circulation.[7,8] Randomized clinical trials have compared vasopressin to standard treatment during cardiac arrest, showing no overall benefit of vasopressin over or in addition to epinephrine.[9]

Glucocorticoids regulates a wide range of functions (such as metabolism, inflammation, and cell proliferation) and has been shown to increase return of spontaneous circulation in animal studies of cardiac arrest.[10] Studies in human subjects has been more limited and in other disease states the effect of glucocorticoids has varied.[11] For example, glucocorticoids have been shown to potentially reduce mortality in septic shock, whereas it has been shown to be harmful in traumatic brain injury.[12–14]

Although a potential synergistic effect of vasopressin and glucocorticoid is unclear, two randomized, double-blind trials, published in 2009 and 2013, studied the effect of vasopressin and glucocorticoids administration compared to placebo during in-hospital cardiac arrest.[15,16] The investigators found a significant improvement in outcomes, including survival at hospital discharge. Despite these findings, the use of vasopressin and glucocorticoids is not recommended as an adjunctive therapy for cardiac arrest by the American Heart Association or the European Resuscitation Council.[4,5] With new evidence available, including the randomized, double-blind "VAM-IHCA" trial, an updated systematic review of the evidence is warranted.[17]

The aim of this study was to perform a systematic review and individual participant data meta-analysis of vasopressin and glucocorticoids for the treatment of cardiac arrest.

Methods

Protocol and registration

The protocol was prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42021255397) on June 18, 2021. The protocol is provided in the Supplementary Content. The reporting of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Individual Patient Data (PRISMA-IPD) guidelines.[18] The PRISMA-IPD checklist is provided in the Supplementary Content.

Eligibility criteria and outcomes

The study question was framed using the PICO (Population, Intervention, Comparison, Outcome) format: In adult patients with cardiac arrest in any setting (out-of-hospital or in-hospital), does vasopressin and glucocorticoids provided during cardiac arrest, as compared to no vasopressin and no glucocorticoids, improve clinical outcomes?

Outcomes were prioritized by the authors based on the available literature. We included return of spontaneous circulation, survival at hospital discharge, favorable neurological outcome at hospital discharge, and survival after hospital discharge. A favorable neurological outcome was defined as a Cerebral Performance Category of 1 or 2. Return of spontaneous circulation was considered the primary outcome as post-cardiac arrest interventions were known to differ between previously identified trials (see the "study overview" section in the results).[15,16,19]

We included controlled trials in humans including randomized and non-randomized trials. Observational studies, ecological studies, case series, case reports, reviews, abstracts, editorials, comments, letters to the editor, and unpublished studies were not included. All years and all languages were included if there was an English abstract or an English full-text article.

Information sources and search strategy

On September 30, 2021, we searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials. The search included various text and indexing terms for cardiac arrest, vasopressin, and glucocorticoids. The Cochrane sensitivity-maximizing search strategy was used to identify controlled trials.[20] The search strategies are provided in the protocol. The bibliographies of included articles were reviewed for potential additional articles. To identify registered planned, ongoing, or unpublished trials, we searched the International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.Gov on September 11, 2021. Details are provided in the Supplementary Methods.

Study selection

Two reviewers independently screened all titles and abstracts retrieved from the systematic search. Any disagreement regarding the inclusion or exclusion of publications were resolved via discussion between the reviewers and with a third reviewer as needed. Two reviewers independently reviewed the full texts of all potentially relevant publications passing the first level of screening. Any disagreement regarding eligibility was resolved via discussion. The Cohen's Kappa for inter-observer variance were calculated.

Data extraction

Two reviewers extracted general information from each manuscript using a pre-defined standardized data extraction form. Any discrepancies in the extracted data were identified and resolved via discussion.

Authors of all identified trials were contacted to provide raw individual level data. The data were reviewed for completeness (i.e., missing data, inconsistencies with the peer-reviewed article, and extreme values) and a standardized data format was generated for all the trials.

Risk of bias in individual studies

Two reviewers independently assessed the risk of bias for individual trials using version 2 of the Cochrane risk-of-bias tool for randomized trials.[21] Risk of bias was assessed per outcome. Disagreements were resolved via discussion.

Individual participant data meta-analyses

Trials were evaluated for clinical (i.e., participants, interventions, and outcomes) and methodological (i.e., study design and risk of bias) heterogeneity. Statistical heterogeneity was assessed using forest plots and I-squared statistics.[20] Chi-squared statistics were not considered as the number of trials eligible for data synthesis were small.[22]

Individual participant data were analyzed on a modified intention-to-treat principle only including patients receiving the first dose of the trial drug as well as meeting all the inclusion and exclusion criteria of the individual trials. Fixed effects analyses were conducted as the

primary analyses given the low number of trials.[23] Random effects analyses were conducted as sensitivity analyses by specifying random intercepts and slopes for the individual trials. Logistic regression was used with adjustment for the individual trial and key covariates known to be associated with outcomes including age (linear continuous variable[24]), cardiac arrest location within the hospital (intensive care unit vs. no intensive care unit), time of day (daytime or nighttime), witnessed status (yes or no), and the initial rhythm (shockable or non-shockable).[25] The results were reported as odds ratios with 95% confidence intervals.

Prespecified subgroup analyses were conducted according to age (linear continuous and categorical dichotomized by the median), witnessed status (yes or no), the initial rhythm (shockable or non-shockable), the time from cardiac arrest to trial drug (linear continuous and categorical dichotomized by the median), and the cardiac arrest cause (presumed cardiac or non-cardiac). The location of the cardiac arrest (intensive care unit or not intensive care unit) was added as a post hoc subgroup. The subgroup analyses were conducted with adjustment for the individual trials and key covariates as described above.

SAS software, version 9.4 (SAS Institute, Cary, NC, USA) was used for the analyses.

Bayesian analyses

Bayesian analyses were conducted using individual participant data. The posterior probabilities that the intervention effect exceeded an odds ratio of 1.0, 1.1., and 1.2 or was beneath an odds ratio of 1.0, 0.9, and 0.8 were estimated assuming a range of prior probability distributions.[26]

Priors were specified to reflect a range of beliefs (the mean of the expected treatment effect) for various outcomes based on clinical reasoning. The priors included a non-informative, skeptical (no effect), optimistic (beneficial effect), and pessimistic (harmful effect) belief.[27] The strength of each informative belief (the variance of the expected treatment effect) was characterized as strong, moderate, or weak, allowing for 5%, 15%, and 30% of harm or benefit, respectively. All priors were prespecified using a standardized approach and assumed a normal distribution on the log odds scale.[27] Additional details are provided in Table S1 and in the protocol.

The Bayesian analyses were conducted using Markov Chain Monte Carlo procedures with one chain, 10,000 burn-ins, 1,000,000 iterations, and a thinning rate of 100 to reduce sample autocorrelation.[28] The results are summarized as a graphical presentation of priors and posteriors, mean odds ratios and 95% highest posterior density (HPD) credible intervals, and the probability of any significant benefit and harm. The 95% HPD credible interval refers to the interval enclosing 95% of the posterior distribution around the mode. For symmetrical posterior distributions, the 95% HDP credible interval is equivalent to the equal-tail 95% credible interval.[29]

SAS software, version 9.4 (SAS Institute, Cary, NC, USA) was used for the Bayesian analyses.

Confidence in cumulative evidence

The certainty of the overall evidence for a given outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and classified within one of four categories: very low, low, moderate, or high certainty of evidence.[30] GRADEpro (McMaster University, 2020) was used for drafting of the GRADE tables.

Results

Study overview

The search identified 47 unique records of which three randomized trials published in 2009, 2013, and 2021 were included in the manuscript (Kappa = 0.85) (Fig. S1).[15–17] Two registered trials were identified on ICTRP or ClinicalTrials.Gov comparing the use of vasopressin and glucocorticoids to placebo in in-cardiac arrest (Sweden) and out-of-hospital cardiac arrest (South Korea) (Table S2).

All three included trials compared the combination of glucocorticoids (40 mg methylprednisolone once) and vasopressin (20 IU for a maximum of four or five doses) to placebo during in-hospital cardiac arrest in adult patients receiving at least one dose of epinephrine. Vasopressin and glucocorticoids were administered in addition to standard care according to international guidelines. Two trials were conducted in Greece and one trial was conducted in Denmark. There was some heterogeneity in the post-cardiac arrest interventions. The two trials published in 2009 and 2013 administered hydrocortisone (300 mg daily) to resuscitated patients with circulatory shock in the intervention arm, whereas the trial published in 2021 did not include any protocolized post-cardiac arrest interventions (Table S3).

There were some differences in patient characteristics between the three trials (Table 1). Compared to the 2021 trial, patients in the 2009 and 2013 trials more often had a cardiac arrest that was witnessed (2009-trial: 81%, 2013-trial: 92%, 2021-trial: 74%), occurred in the intensive care unit (2009-trial: 31%, 2013-trial: 38%, 2021-trial: 8%), and presented with an initial rhythm of asystole (2009-trial: 61%, 2013-trial: 67%, 2021-trial: 35%).

All trials were assessed as having a low risk of bias for all outcomes (Table S4).

Individual participant data meta-analyses

Individual participant data were obtained from all three trials yielding a combined sample size of 869 patients. Data were pooled for return of spontaneous circulation, survival at hospital discharge, and favorable neurological outcome at hospital discharge. The 2013 trial also reported survival at one year, whereas the 2021 trial reported survival, favorable neurological outcome, and health-related quality of life at 30 and 90 days. Results from individual trials, meta-analyses, and statistics of heterogeneity are presented in Fig. 1.

The results favored vasopressin and glucocorticoids as compared to placebo for return of spontaneous circulation (odds ratio: 2.09, 95% CI: 1.54 to 2.84). The estimates for survival at hospital discharge (odds ratio: 1.39, 95%CI: 0.90 to 2.14) and favorable neurological outcome (odds ratio: 1.64, 95%CI, 0.99 to 2.72) were more uncertain. The results remained largely consistent in the random effects analyses, although the confidence intervals were wider (Fig. S2)

Subgroup analyses were conducted according to age, witnessed status, the initial rhythm, the time to trial drug, the cardiac arrest cause, and the location. There was no effect modification in these subgroups for any of the outcomes (all P values > 0.05) (Fig. 2 and Figs. S3 and S4). When considering age as a continuous variable, there was no effect measure modification for any of the outcomes (Fig. S5 and Table S5). When time to trial drug was treated as a continuous variable, there was no effect measure modification for return of spontaneous circulation, but the odds ratio for survival at hospital discharge (change in odds ratio per one minute: 0.85, 95%CI: 0.76 to 0.94) and favorable neurological

outcome (change in odds ratio per one minute: 0.86, 95%CI: 0.76 to 0.98) decreased over time, indicating that the potential beneficial effect diminished with longer times to trial drugs (Fig. S5 and Table S5).

Bayesian analyses

The Bayesian analyses assuming a non-informative prior were consistent with the primary analyses (Table 2). The posterior odds ratio was estimated at 2.13 (95% credible interval: 1.51 to 2.82) for return of spontaneous circulation, 1.39 (95% credible interval: 0.81 to 2.00) for survival at hospital discharge, and 1.65 (95% credible interval: 0.91 to 2.45) for favorable neurological outcome (Fig. S6).

In the case of a strongly optimistic prior, the posterior odds ratio was estimated at 1.68 (95% credible interval: 1.31 to 2.05) for return of spontaneous circulation, at 1.24 (95% credible interval: 1.02 to 1.49) for survival at hospital discharge, and at 1.27 (95% credible interval: 1.02 to 1.52) for favorable neurological outcome. In the case of a strongly pessimistic prior, the posterior odds ratio was estimated at 1.30 (95% credible interval: 1.03 to 1.59) for return of spontaneous circulation, at 0.93 (95% credible interval: 0.76 to 1.11) for survival at hospital discharge, and at 0.93 (95% credible interval: 0.75 to 1.11) for favorable neurological outcome.

A graphical presentation of the Bayesian results is provided in Fig. S7 for return of spontaneous circulation, in Fig. 3 for survival at hospital discharge, and in Fig. S8 for favorable neurological outcome. The corresponding posterior probabilities for benefit (an odds ratio > 1.0, >1.1, and >1.2) and harm (an odds ratio < 1.0, <0.9, and <0.8) are provided in Tables S6 and S7. For example, the probability that the odds ratio was above 1.0 (i.e., representing a beneficial effect) was 99% in the case of a strong optimistic prior, 84% in the case of a strong skeptical prior, and 22% in the case of a strong pessimistic prior for survival to hospital discharge.

Table 1 – Patient characteristics of included trials.

	2009-trial (N = 100)	2013-trial (N = 268)	2021-trial (N = 501)	Total (N = 869)
Patient characteristics				
Age – years	73 (58, 79)	68 (54, 76)	72 (64, 79)	72 (60, 78)
Sex – male	59 (59)	183 (68)	322 (64)	564 (65)
Cardiac arrest characteristics				
Cause of cardiac arrest				
Presumed cardiac[a]	40 (40)	69 (26)	143 (29)	252 (29)
Non-cardiac	60 (60)	199 (74)	358 (71)	617 (71)
Location				
Intensive care unit	31 (31)	101 (38)	41 (8)	173 (20)
Not intensive care unit	69 (69)	167 (62)	460 (92)	696 (80)
Initial rhythm				
Asystole	61 (61)	180 (67)	177 (35)	418 (48)
PEA	25 (25)	43 (16)	272 (54)	340 (39)
VF/VT	14 (14)	45 (17)	52 (10)	111 (13)
Time of day[b]				
Nighttime	35 (35)	82 (31)	167 (33)	284 (33)
Daytime	65 (65)	186 (69)	334 (67)	585 (67)
Day of week[c]				
Weekday	62 (62)	199 (74)	363 (72)	624 (72)
Weekend	38 (38)	69 (26)	138 (28)	245 (28)
Witnessed	81 (81)	247 (92)	370 (74)	698 (80)
Monitored	35 (35)	111 (41)	208 (42)	354 (41)
Post-cardiac arrest characteristics				
TTM	11 (11)	66 (25)	37 (19)	114 (20)
Coronary catherization	9 (9)	30 (11)	32 (6)	71 (8)
PCI	6 (6)	18 (7)	17 (3)	41 (5)
Trial characteristics				
Assigned to intervention	48 (48)	130 (49)	237 (47)	415 (48)
Assigned to placebo	52 (52)	138 (51)	264 (53)	454 (52)
Time to study drug – min	3 (2, 5)	5 (3, 6)	8 (6, 12)	6 (4, 11)
Outcomes				
Return of spontaneous circulation	66 (66)	200 (75)	186 (37)	452 (52)
Survival at hospital discharge	11 (11)	31 (12)	56 (11)	98 (11)
CPC 1 or 2 at hospital discharge	10 (10)	25 (9)	35 (7)	70 (8)

Abbreviations: PEA, pulseless electrical activity; VF, ventricular fibrillation; VT, ventricular tachycardia; TTM, targeted temperature management; PCI, percutaneous coronary intervention; CPC, Cerebral Performance Category;

[a] Presumed cardiac or unknown cause.

[b] Nighttime refers to 11.00 PM to 6.59 AM; Daytime refers to 7.00 AM to 10.59 PM.

[c] Weekday refers to Monday 00.01 AM to Friday 11.59 PM; Weekend refers to Saturday 00.01 AM to Sunday 11.59 PM.

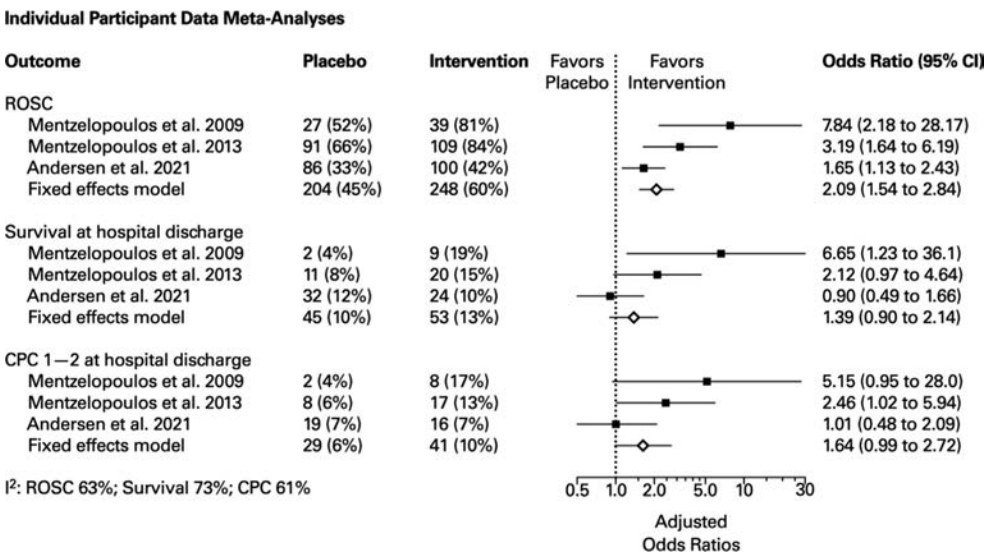

Fig. 1 – Meta-analyses using individual participant data. An overview of adjusted results from individual randomized trials and fixed effects analyses. The dots and solid lines represent odds ratios with 95% confidence intervals. The dashed line represents no association between vasopressin and glucocorticoids and outcomes. Abbreviations: ROSC, return of spontaneous circulation; CPC, Cerebral Performance Category; 95% CI, 95% confidence interval.

Certainty in evidence

The overall certainty in evidence for vasopressin and glucocorticoids as compared to placebo was assessed as moderate for return of spontaneous circulation, low for survival at hospital discharge, and low for favorable neurological outcome at hospital discharge (Table S8).

Discussion

This systematic review and individual participant data meta-analysis included three randomized trials comparing the use of vasopressin and glucocorticoids to placebo during in-hospital cardiac arrest. Results favored vasopressin and glucocorticoids for return of spontaneous circulation but were more uncertain for survival at hospital discharge and favorable neurological outcomes.

Two randomized trials were published by Mentzelopoulos et al. in 2009 and 2013 assessing the potential beneficial effect of vasopressin and glucocorticoids in cardiac arrest as compared to placebo.[15,16] Both trials found a significant improvement in return of spontaneous circulation, survival at hospital discharge, and favorable neurological outcome. Nonetheless, primarily due to the lack of external validation, the use of vasopressin and glucocorticoids is not recommended in clinical practice.[4,5] A separate trial comparing vasopressin and glucocorticoids to placebo was recently published by Andersen et al. in 2021.[17] Although that trial found a similar benefit on return of spontaneous circulation as the trials by Mentzelopoulos et al., the authors found no significant differences in mid-term survival between the two interventions arms. The discrepancy in results could potentially be explained by heterogeneity in post-cardiac arrest interventions (i.e., the use of hydrocortisone to patients with circulatory shock), patient baseline characteristics (e.g., age, initial rhythm, and cardiac arrest location), and the time to trial drug administration. For example, compared to the 2021-trial, the earlier trials provided hydrocortisone (300 mg daily for up to seven days) to approximately 70% of resuscitated patients with circulatory shock in the intervention arm. Consequently, the pooled results for survival at hospital discharge and favorable neurological outcome should be interpreted with some caution.

We obtained individual participant data from all identified trials. Individual participant data are considered the gold-standard for meta-analyses and have the advantage of allowing for standardized analyses, increased statistical power for assessing interactions of subgroups, and adjustment for between-study heterogeneity.[31] As such, we were able to adjust for some of the heterogeneity across trials by including key covariates known to differ between the trials and be associated with the outcomes in the models. Our adjusted analyses were largely consistent with the results of the most recent largest trial by Andersen et al. showing an improvement in return of spontaneous circulation but more uncertain results for the remaining outcomes. We did find a signal towards benefit for favorable neurological outcome at hospital discharge in our analyses (odds ratio: 1.64, 95%CI, 0.99 to 2.72), although the confidence intervals were wide and crossed one. Given that there were a relatively small number of patients alive at hospital discharge to provide statistical power to reliably detect a difference between groups, the confidence for this outcome was assessed as low (Table S8).

We aimed to explore heterogeneity in the treatment effect for several subgroups. Although there was no clear effect measure modification in our primary subgroup analyses (Fig. 2), additional analyses treating time to trial drug as a continuous variable, suggested that the potential beneficial effect of the intervention diminished with increasing time to drug administration (Fig. S5). Although these findings are merely hypothesis generating, they suggest that future trials should

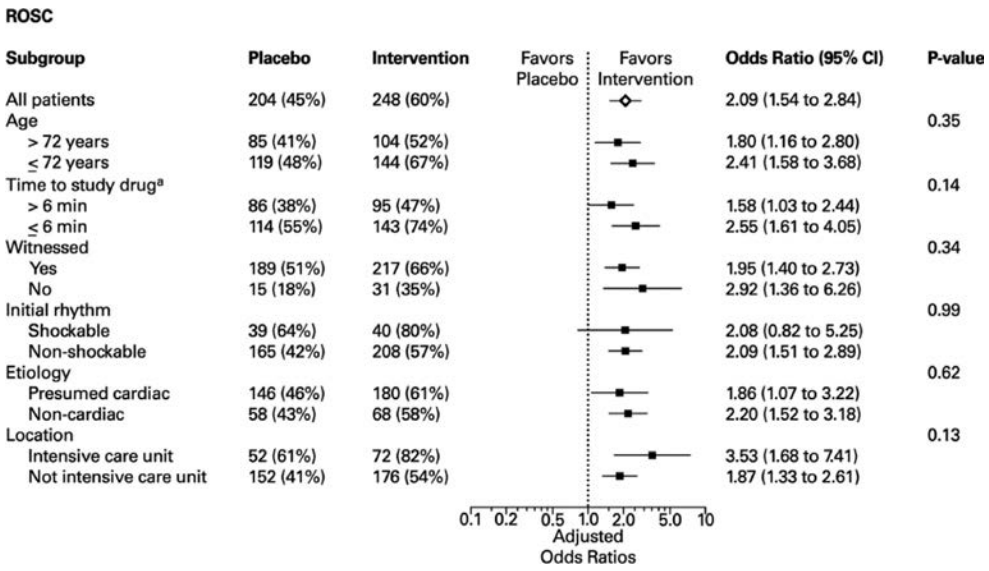

Fig. 2 – Subgroup analyses for return of spontaneous circulation. An overview of adjusted subgroup analyses for return of spontaneous circulation. The dots and solid lines represent odds ratios with 95% confidence intervals. The dashed line represents no association between vasopressin and glucocorticoids and the outcome. The P value is the P value for the subgroup interaction. Abbreviations: ROSC, return of spontaneous circulation; CPC, Cerebral Performance Category; 95% CI, 95% confidence interval. [a] Missing for 19 patients in the 2009 trial and for 21 patients in the 2013 trial.

Table 2 – Posterior estimates from Bayesian analyses.

Prior belief	Posterior mean odds ratio (95% credible interval)		
	ROSC	Survival	CPC 1–2
Non-informative	2.13 (1.51 to 2.82)	1.39 (0.81 to 2.00)	1.65 (0.91 to 2.45)
Skeptical			
Strong	1.63 (1.26 to 2.05)	1.17 (0.85 to 1.51)	1.22 (0.86 to 1.58)
Moderate	1.89 (1.39 to 2.43)	1.30 (0.85 to 1.79)	1.42 (0.91 to 1.99)
Weak	2.02 (1.46 to 2.65)	1.35 (0.88 to 1.93)	1.54 (0.90 to 2.31)
Optimistic			
Strong	1.68 (1.31 to 2.05)	1.24 (1.02 to 1.49)	1.27 (1.02 to 1.52)
Moderate	1.85 (1.40 to 2.34)	1.29 (0.96 to 1.63)	1.33 (0.96 to 1.71)
Weak	2.04 (1.47 to 2.66)	1.35 (0.89 to 1.79)	1.52 (0.90 to 2.18)
Pessimistic			
Strong	1.30 (1.03 to 1.59)	0.93 (0.76 to 1.11)	0.93 (0.75 to 1.11)
Moderate	1.61 (1.21 to 2.03)	1.05 (0.79 to 1.34)	1.05 (0.77 to 1.37)
Weak	1.90 (1.35 to 2.47)	1.21 (0.77 to 1.68)	1.30 (0.83 to 1.85)

Abbreviations: ROSC, return of spontaneous circulation; CPC, Cerebral Performance Category.

aim to provide the intervention as soon as feasible to optimize the chance of detecting a beneficial effect.

When interpreting a treatment effect using a frequentist approach, a non-significant result may be conflicting with a clinical intuition of no association (and vice versa). The Bayesian framework constitutes an alternative to conventional frequentist statistics by specifying the probability of a specific treatment effect by incorporating a range of beliefs as priors.[27] In this study, we demonstrated that across a range of prior beliefs about the probability of benefit from using vasopressin and glucocorticoids, the posterior probability of return of spontaneous circulation (odds ratio > 1.0) ranged from 99% to 100% and the probability for survival at hospital discharge and favorable neurological outcome ranged from 22% to 99% (Table S4). Notably, even in the case of a strongly pessimistic prior belief, the use of vasopressin and glucocorticoids remained significantly associated with return of spontaneous circulation (odds ratio: 1.30; 95% credible interval: 1.03 to 1.59). Moreover, in the case of a strongly optimistic prior belief, the use of vasopressin and glucocorticoids was associated with both improved survival at hospital discharge (odds ratio: 1.27; 95% credible interval: 1.02 to 1.52) and favorable neurological outcome (odds ratio: 1.27; 95% credible interval: 1.02 to 1.52). Whether these findings support the use of vasopressin and glucocorticoids as an adjunct therapy during cardiac arrest depend on prior beliefs, the probability of benefit and harm,

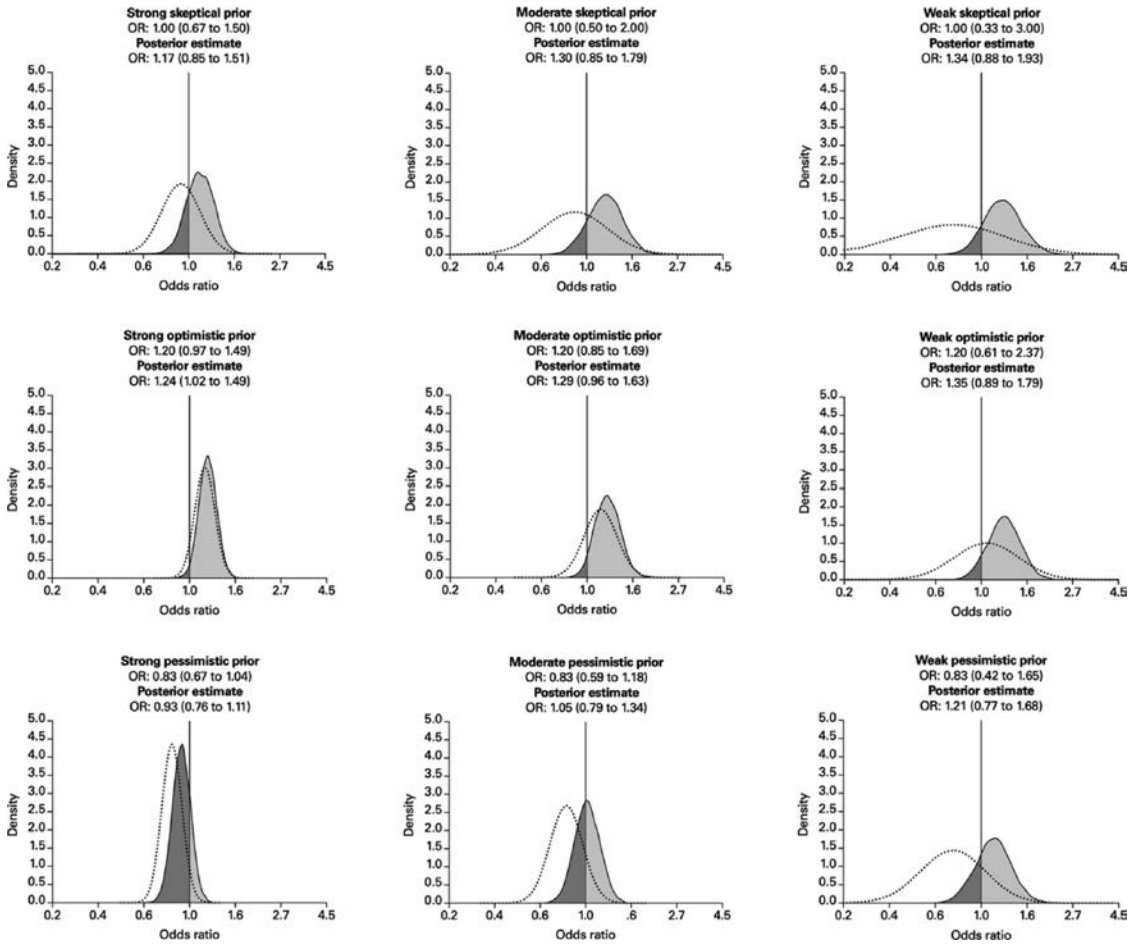

Fig. 3 – Bayesian analyses for survival at hospital discharge. An overview of posterior estimates for survival at hospital discharge assuming a range of prior beliefs. The dashed curve represents the prior probability distribution. The shaded curve represents the posterior probability distribution. Odds ratios > 1.0 indicate benefit and odds ratios < 1.0 indicate harm. The X-axis represents odds ratios on the natural logarithmic scale. The Y-axis represents the probability density. Note that the top of the distribution (the mode) does not correspond to the mean as the distribution is log normal.

as well as other factors such as cost-effectiveness and the effect on other outcomes.

This review should be interpreted in the context of the following limitations. First, the analyses were limited by the data and sample sizes inherent to the individual trials. We may, therefore, have been underpowered to detect small but clinically significant effects in mid-term and long-term outcomes. Second, there was some heterogeneity between the included trials which could not be accounted for in the pooled analyses why the results, especially outcomes at hospital discharge, should be interpreted carefully. Third, we prespecified a range of prior beliefs for the Bayesian analyses and different priors would have led to different posterior estimates.

Considering there was similar benefit on return of spontaneous circulation in all three trials but a lack of effect on survival in the 2021 trial, it can be speculated whether this is caused by the earlier trials providing hydrocortisone in resuscitated patients with circulatory shock. Future trials should consider including post-cardiac arrest glucocorticoids, potentially in a factorial design.

In conclusion, among adult patients with an in-hospital cardiac arrest, the use of vasopressin and glucocorticoids when compared to placebo, resulted in improved return of spontaneous circulation. Larger trials are needed to determine whether there is an effect on longer-term survival and favorable neurological outcome.

Declaration of Competing Interest

All authors have been involved in previous trials comparing the use of vasopressin and glucocorticoids to placebo in cardiac arrest (ClinicalTrials.Gov: NCT00411879, NCT00729794, and NCT03640949). Dr Andersen reported nonfinancial support from Amomed Pharma GmbH, which provided the trial drug during the conduct of the VAM-IHCA trial. Dr Granfeldt reported receiving personal fees from Noorik Biopharmaceuticals outside the conduct of the VAM-IHCA trial. The Scientific Council of Evaggelismos General Hospital granted permission to Dr. Mentzelopoulos for sharing of the

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2021.12.030.

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