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Vasopressin for cardiac arrest: Meta-analysis of randomized controlled trials☆

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ABSTRACT

Background: Prior meta-analyses-reported results of randomised controlled trials (RCTs) published between 1997 and 2004 failed to show any vasopressin-related benefit in cardiac arrest. Based on new RCT-data and a hypothesis of a potentially increased vasoconstricting efficacy of vasopressin, we sought to determine whether the cumulative, current evidence supports or refutes an overall and/or selective benefit for vasopressin regarding sustained restoration of spontaneous circulation (ROSC), long-term survival, and neurological outcome.
Methods: Two reviewers independently searched PubMed, EMBASE, and Cochrane Database for RCTs assigning adults with cardiac arrest to treatment with a vasopressin-containing regimen (vasopressin-group) vs adrenaline (epinephrine) alone (control-group) and reporting on long-term outcomes. Data from 4475 patients in 6 high-methodological quality RCTs were analyzed. Subgroup analyses were conducted according to initial cardiac rhythm and time from collapse to drug administration (T_{DRUG}) < 20 min.
Results: Vasopressin vs. control did not improve overall rates of sustained ROSC, long-term survival, or favourable neurological outcome. However, in asystole, vasopressin vs. control was associated with higher long-term survival {odds ratio (OR) = 1.80, 95% confidence interval (CI) = 1.04–3.12, $P = 0.04$}. In asystolic patients of RCTs with average T_{DRUG} < 20 min, vasopressin vs. control increased the rates of sustained ROSC (data available from 2 RCTs; OR = 1.70, 95% CI = 1.17–2.47, $P = 0.005$) and long-term survival (data available from 3 RCTs; OR = 2.84, 95% CI = 1.19–6.79, $P = 0.02$).
Conclusions: Vasopressin use in the resuscitation of cardiac arrest patients is not associated with any overall benefit or harm. However, vasopressin may improve the long-term survival of asystolic patients, especially when average T_{DRUG} is <20 min.

1. Introduction

Each year, more than 600,000 people in North America and Europe experience sudden death.[1] Cardiac arrest is a major public health problem with a very poor prognosis, especially in patients requiring vasopressors.[1–3] Recently reported survival rates for vasopressor-treated cardiac arrest are within 2–20%.[1,2,4–6]

Adrenaline (epinephrine) remains the vasopressor drug of choice in cardiac arrest.[3] Epinephrine increases myocardial oxygen consumption during cardiopulmonary resuscitation (CPR) and causes myocardial dysfunction after restoration of spontaneous circulation (ROSC).[7–9] Vasopressin has been suggested as an alternative, potent vasopressor. Vasopressin causes contraction of vascular smooth muscle through stimulation of the V1a receptors and increases smooth muscle responsiveness to catecholamines.[10] Endogenous vasopressin levels are higher in patients achieving ROSC.[11] Furthermore, prior experimental data suggest that vasopressin improves vital organ perfusion during CPR, post-ROSC survival, and neurological recovery.[12–17]

Despite the promising laboratory and preliminary clinical data,[12–18] prior, large, randomised, controlled trials (RCTs) comparing vasopressin and epinephrine failed to show any clear, overall advantage for vasopressin.[4,19] Accordingly, preceding meta-analyses of RCTs published between 1997 and 2004 concluded that "available evidence cannot support the inclusion of vasopressin in CPR protocols".[20,21] However, the enrollment of patients

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with virtually no chance of survival may affect RCT results.[22,23] Besides previously meta-analyzed and inconclusive data,[20,21] 4 RCTs assessing vasopressin efficacy in 100–2894 patients have been published between 2006 and 2009.[1,2,24,25] Results were either neutral,[1,24,25] or favored vasopressin use.[2]

In the presence of new RCT-data and a hypothesis of an increased vasoconstricting efficacy of vasopressin-containing regimens during CPR,[2,26] we undertook the present meta-analysis. We sought to determine whether the cumulative, current evidence supports or refutes a possible, overall and/or selective benefit for vasopressin with respect to sustained ROSC, long-term survival, and neurological outcome.

2. Methods

2.1. Data sources

We searched PubMed (articles archived until June 2010), EMBASE and Cochrane Central Register of Controlled Trials. Our search strategy is detailed in the electronic supplement (eSupplement).

2.2. Study selection

Literature search and study selection were performed independently by 2 reviewers (IS and SDM). An RCT was potentially eligible if it compared a vasopressin-containing regimen (vasopressin group) to epinephrine alone (control group) for adult, out-of-hospital or in-hospital cardiac arrest, and reported on survival. We set no restrictions on publication time. We excluded publications not providing original data (i.e. reviews, meta-analyses, comments, letters, and guidelines), case reports, animal studies, and observational studies. We also excluded studies published only as abstracts and non-English studies,[21] and studies fulfilling a pre-specified criterion for "high risk of bias"[27] (see eSupplement). Fig. 1 illustrates the study selection process. Any potential disagreements were resolved by discussion/consensus.[20]

2.3. Data extraction

The 2 reviewers (IS and SDM) used standardized, electronic, data-collection forms[28,29] to independently collect the following data: first author, publication year, RCT geographic location(s), study design, and baseline characteristics of enrolled patients. The reviewers also gathered information regarding whether the cardiovascular collapse was witnessed, performance of bystander CPR and other co-interventions (e.g. use of amiodarone[30] or thrombolytics[31,32] during CPR, or post-ROSC therapeutic hypothermia[33,34]), times from collapse to basic life support (BLS) and advanced life support (ALS), ALS duration, study drugs {including route of administration, dosage, and time from cardiovascular collapse to first study-drug injection (T_{DRUG})}, and initial cardiac rhythm. In addition, the reviewers documented the number of any randomised patients excluded from the analysis and the reason(s) for such exclusion(s), collected data on ROSC, survival, and neurological outcome, and summarised the key study conclusions. Lastly, the authors of included studies were contacted for data not reported in the respective articles.

2.4. Data synthesis and definitions of outcomes

We chose to pool data on clinically meaningful, short-term and long-term outcomes, which are commonly pre-specified by protocols of cardiac arrest trials. Outcome measures were defined as follows: sustained ROSC: patient achieves restoration and maintenance of spontaneous circulation for ≥15 min[2,19] (in-hospital trials) or until hospital admission[18,35] (out-of-hospital trials); long-term survival: patient survives to ≥30 days post-randomization or leaves the acute care institution alive (i.e. survives to hospital discharge); favourable neurological outcome: patient achieves long-term survival and has a Glasgow–Pittsburgh Cerebral Performance Category (CPC) score of 1 (i.e. good cerebral performance,[36] see also the eSupplement} or 2 (i.e. moderate cerebral disability[36]; eSupplement).

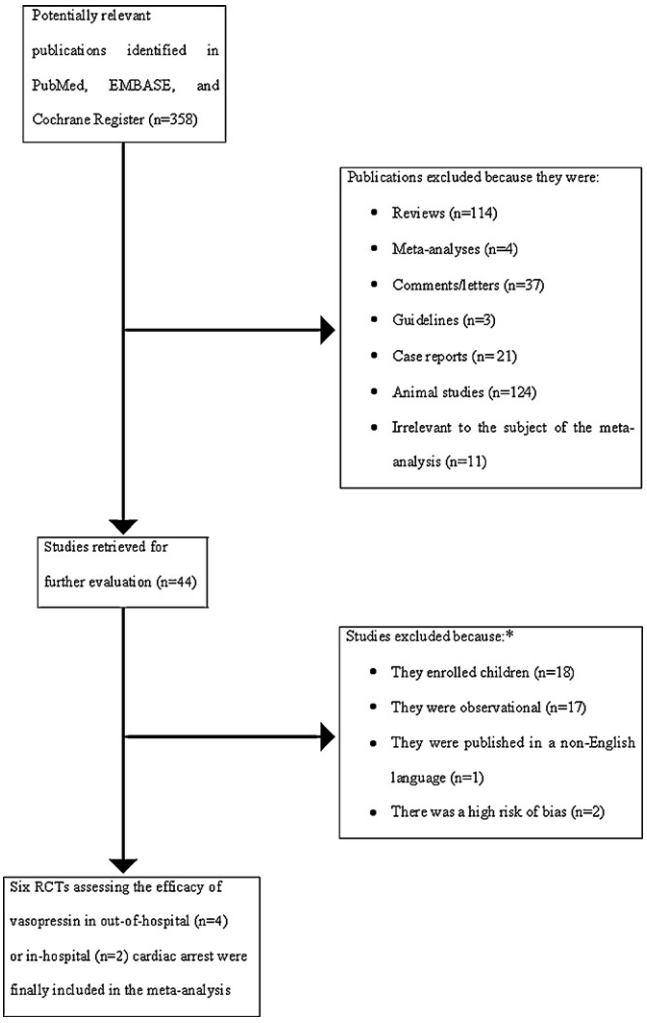

Fig. 1. Flow diagram of the study selection process. *1 additional study was excluded, because it was published only in abstract form (see Section 2); the results of this study were retrieved from Ref. 20 and were used in the sensitivity analyses (see also Section 2 and the electronic supplement).

2.5. Statistical analysis

We performed an intention-to-treat analysis with Review Manager (RevMan version 5.0.1; Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2008). We assessed heterogeneity among RCTs with the I^2 statistic (20). We set cut-off points of $I^2 \leq 25\%$, I^2 within 26–49%, and $I^2 \geq 50\%$ to define low, moderate, and statistically significant heterogeneity, respectively.[37,38] We chose odds ratios (ORs) and 95% confidence intervals (CI) as effect measures.[21,38] In all analyses, whenever there was a moderate or statistically significant heterogeneity among RCTs, we analyzed the data with the DerSimonian–Laird random effects method.[39] When heterogeneity was low, we analyzed the data with

the Mantel–Haenszel fixed effect method.[40] We did not search for publication bias, because the included RCTs were <10.[41]

A prior meta-analysis identified the initial cardiac rhythm as a major factor of long-term survival variation across studies.[20] Accordingly, in a pre-specified subgroup analysis, we assessed the effect of vasopressin in the asystole, ventricular fibrillation/tachycardia (VF/VT), and pulseless electrical activity (PEA) subgroups of the included studies.[38] Also, based on in-hospital and out-of-hospital results on post-ROSC diastolic arterial pressure,[2,42] we conducted an additional subgroup analysis according to "initial rhythm and T_{DRUG} < 20 min." Lastly, we conducted sensitivity analyses to determine whether the inclusion of excluded RCTs would have affected the results of our primary analysis.[38]

3. Results

3.1. Characteristics of the included studies

Table 1 displays the main characteristics of the 6 included RCTs, and of 2 RCTs excluded due to high risk of bias. The kappa statistic for included RCTs was 1.0. Four RCTs took place in Europe[1,2,4,19] and 2 in North America.[19,25] Four RCTs (3 multi-centre and 1 single-centre) reported on out-of-hospital cardiac arrest[1,4,18,25] and 2 (1 multi-centre and 1 single-centre) on in-hospital cardiac arrest.[2,19] Included RCT methodological quality was high, with low probability of bias (for details see eSupplement).

3.1.1. Witnessed arrest, presenting rhythm, and times from collapse to intervention

The average reported frequency of witnessed cardiac arrest was 70.4% (range: 45.2–81.0%). There was no between-group difference in witnessed arrest frequency in any of the included studies. In the pooled population of 4745 patients, 3512 (74.0%) had a witnessed arrest. The initial cardiac rhythm was asystole in 3210 patients (67.7%), VF/VT in 924 patients (19.5%), and PEA in 609 patients (12.8%); in 1 study,[19] the initial cardiac rhythm was not reported for 2 patients; in another study,[18] only patients with VF/VT were enrolled. The average times from cardiovascular collapse to BLS and ALS, and average T_{DRUG} were respectively within 6–8 and 15–17 min, and 15–22 min in the out-of-hospital studies[1,4,18,25]; these response times were respectively ≤1–2 and ≤3, and ≤5–6 min in the in-hospital studies.[2,19]

3.1.2. Assessed intervention

In 3 studies, 40 IU of vasopressin were given either as soon as a vasopressor drug was indicated according to contemporary resuscitation guidelines,[18,19] or as "soon as possible" after the first dose of epinephrine.[25] In 1 study,[4] vasopressin-group patients received up to 2 doses of 40 IU of vasopressin, followed by epinephrine if ROSC was not achieved. In 1 study,[1] vasopressin-group patients received up to 2 doses of combined 40 IU of vasopressin and 1 mg of epinephrine, followed by epinephrine if ROSC was not achieved. In 1 study,[2] vasopressin-group patients received up to 5 doses of combined 20 IU of vasopressin and 1 mg of epinephrine, followed by epinephrine if ROSC was not achieved; vasopressin-group patients also received 40 mg of methylprednisolone along with the first dose of the vasopressors, and post-ROSC, stress-dose hydrocortisone if they fulfilled a pre-specified criterion for postresuscitation shock. In all studies, the average vasopressin dose was within 40–80 IU. The average time from ALS initiation to vasopressin administration was ≤5–6 min in 4 studies,[1,2,4,19] approximately 8 min in 1 study,[18] and within 13–14 min in 1 study.[25] Also, mean ALS duration was within 12–38 min. Thus, since vasopressin mean plasma half life is approximately 24 min,[43] its vasopressor effects were likely present throughout ALS. Furthermore, in the pooled vasopressin-group, 2120 of the 2370 patients (89.5%) either received additional epinephrine,[4,18,19] or epinephrine was anyway combined with vasopressin according to study protocol.[1,2,25] Consequently, in the majority of the pooled vasopressin-group patients, results actually reflect the effect of combined vasopressin and epinephrine during CPR.

3.1.3. Co-interventions

These included bystander CPR, pharmacological interventions,[30–32] and therapeutic hypothermia,[33,34] and were generally balanced between vasopressin and control groups of the included studies (for details see eSupplement).

3.1.4. Assessed outcomes

Regarding long-term outcomes, 1 study assessed survival to ≥30 days post-randomisation,[25] 5 studies assessed survival to hospital discharge,[1,2,4,18,19] and 1 study[1] also reported on 1-year survival. Furthermore, 1 study reported the Glasgow Coma score at hospital discharge,[18] and 4 studies reported the CPC score at hospital discharge.[1,2,4,19] Consequently, we analyzed the results of the latter 4 studies with respect to neurological outcome.

3.2. Overall results on the pooled study population

Heterogeneity among studies was either statistically significant (I^2 = 71% for sustained ROSC) or moderate (I^2 = 46% for both long-term survival and neurological outcome). There was no significant difference between the vasopressin group and control group in sustained ROSC (OR = 1.25, 95% CI = 0.90–1.74, P = 0.18; Fig. 2A), long-term survival (OR = 1.13, 95% CI = 0.71–1.78, P = 0.61; Fig. 2B), and favourable neurological outcome (OR = 0.87, 95% CI = 0.49–1.52, P = 0.62; Fig. 2C).

3.3. Subgroup analyses

3.3.1. Initial cardiac rhythm

Due to unavailable subgroup data, we could not assess the effect of vasopressin on neurological outcome in any subgroup. Subgroup data on sustained ROSC and long-term survival were available from 5 studies[1,2,4,18,25] and all 6 studies, respectively. After the elimination of clinical heterogeneity due to initial cardiac rhythm,[20] the statistical heterogeneity of sustained ROSC was significant in asystole (I^2 = 61%) and PEA (I^2 = 60%), but low in VF/VT (I^2 = 19%). Also, the statistical heterogeneity of long-term survival was low in asystole (I^2 = 9%) and VF/VT (I^2 = 16%), but moderate in PEA (I^2 = 44%).

Vasopressin vs. control had no significant effect on sustained ROSC in any of the subgroups (asystole, OR = 1.20, 95% CI = 0.79–1.82, P = 0.39; VF/VT, OR = 1.15, 95% CI = 0.87–1.52, P = 0.33; PEA, OR = 1.09, 95% CI = 0.54–2.18, P = 0.80; detailed results presented in eFig. 1 of the eSupplement). Also, vasopressin compared to control had no significant effect on long-term survival in VF/VT (OR = 0.95, 95% CI = 0.66–1.37, P = 0.77; eFig. 2 of the eSupplement) and PEA (OR = 0.78, 95% CI = 0.24–2.50, P = 0.67; eFig. 2 of the eSupplement). In contrast, in asystole, vasopressin was associated with a more frequent long-term survival relative to control (OR = 1.80, 95% CI = 1.04–3.12, P = 0.04; Fig. 3A). Notably, 12 of the 16 additional survivors (75%) actually originated from 1 asystole subgroup with 30 patients from the study of Mentzelopoulos et al.[2] and 1 asystole subgroup-subdivision with 187 patients from the study of Wenzel et al.[4] During ALS, these 217 patients had received either combined vasopressin-epinephrine[2] or 80 IU of vasopressin followed by additional epinephrine.[4] Also, in both studies, average T_{DRUG} was <20 min (see also below).

A test for heterogeneity on the pooled, subgroup, long-term survival results of the included studies yielded a statistically significant

Table 1
Main characteristics of 8 potentially eligible trials.

First author, reference no.	Year of publication; country	Study design[a]	Study population,[b] (*n*)	Setting	Intervention in vasopressin group[c]	Intervention in control group[c]	Dosage of vasopressin	Number of enrolled patients; male (%)	CPR by bystander- no./total no. (%)[d]	Initial cardiac rhythm (%)
Mentzelopoulos[2]	2009; Greece	Single-centre double-blind RCT	Adult patients (≥18 years) with cardiac arrest (*n* = 100)	In-hospital	Vasopressin and epinephrine and corticosteroids[e]	Epinephrine and placebos	20–100 IU[f]	100; (59%)	Not applicable	VF/VT: 14% PEA: 25% Asystole: 61%
Gueugniaud[1]	2008; France	Multi-centre double-blind RCT	Adult patients (≥18 years) with cardiac arrest (*n* = 2894)	Out-of-hospital	Vasopressin and epinephrine[e]	Epinephrine and placebo	40–80 IU[g]	2894; (74%)	400/1442 (28%) vs 377/1452 (26%)	VF/VT: 9% PEA: 8% Asystole: 83%
Callaway[25]	2006; USA	Multi-centre double-blind RCT	Adult patients (≥18 years) with cardiac arrest (*n* = 325)	Out-of-hospital	Vasopressin and epinephrine[e]	Epinephrine and placebo	40–80 IU[g]	325; (61%)	52/167 (31%) vs 56/158 (35%)	VF/VT: 15% PEA: 22% Asystole: 51%
Wenzel[4]	2004; Austria, Germany, Switzerland	Multi-centre double-blind RCT	Adult patients (≥18 years) with cardiac arrest (*n* = 1186)	Out-of-hospital	Vasopressin followed by epinephrine	Epinephrine and placebo	40–80 IU[g]	1186; (69%)	111/589 (19%) vs 107/597 (18%)	VF/VT: 40% PEA: 16% Asystole: 45%
Stiell[19]	2001; Canada	Multi-centre double-blind RCT	Adult patients (≥16 years) with cardiac arrest (*n* = 200)	In-hospital	Vasopressin followed by epinephrine	Epinephrine and placebo	40 IU[g]	200; (63%)	Not applicable	VF/VT: 21% PEA: 48% Asystole: 31%
Lindner[18]	1997; Germany	Single-centre double-blind RCT	Adult patients (≥18 years) with DC-countershock-refractory VF/VT (*n* = 40)	Out-of-hospital	Vasopressin followed by epinephrine	Epinephrine and placebo	40 IU[g]	40; (73%)	4/20 (20%) vs 5/20 (25%)	VF/VT: 100% PEA: 0% Asystole: 0%
Ducros[42,h]	2010; France	Single-centre double-blind RCT	Adult patients with witnessed cardiac arrest (*n* = 44)	Out-of-hospital	Vasopressin and epinephrine with/without nitroglycerin[e]	Epinephrine and placebos	40–120 IU[g]	44; (86%)	9/28 (32%) vs 7/16 (44%)	VF/VT: 14% PEA: 32% Asystole: 55%
Mukoyama[24,h]	2009; Japan	Single-centre RCT	Adult patients (≥18 years) with cardiac arrest of presumed cardiac etiology (*n* = 336)	Out-of-hospital	Vasopressin	Epinephrine	40–160 IU[g]	336; (71%)	25/178 (14%) vs 26/158 (17%)	VF/VT: 24% PEA: 14% Asystole: 62%

RCT, randomised controlled trial; IU, international unit; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity.

[a] All studies were prospective.

[b] All patients required vasopressor therapy according to contemporary guidelines for resuscitation.

[c] Drugs were administered exclusively intravenously in all studies.

[d] Data presented as vasopressin group vs. control group.

[e] Vasopressin and epinephrine were administered concurrently in these studies.

[f] Each bolus dose of Vasopressin was equal to 20 IU.

[g] Each bolus dose of Vasopressin was equal to 40 IU.

[h] Study excluded from the primary analysis due to "high risk of bias" (see also Section 2 and the electronic supplement).

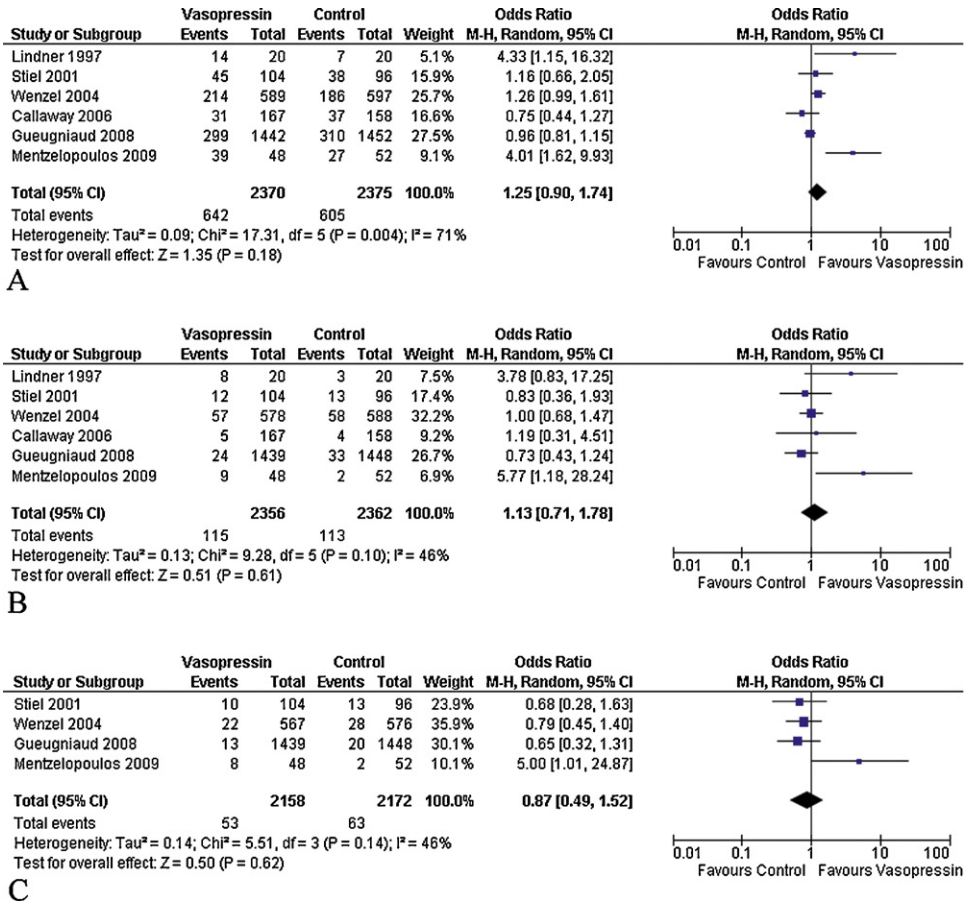

Fig. 2. Overall results of the primary analysis. (A) Sustained restoration of spontaneous circulation; (B) long-term survival; (C) favourable neurological outcome; for respective definitions see Section 2.

I^2 value of 66% (Fig. 3B). This indicates that the apparent difference among the pooled, subgroup ORs cannot be attributed to chance.[21]

3.3.2. *Initial cardiac rhythm and T_{DRUG}*

A recent out-of-hospital study showed no difference between vasopressin and control in diastolic, intra-arterial pressure at 15 min post-ROSC.[42] In that study, average T_{DRUG} exceeded 20 min. In contrast in our in-hospital study,[2] average T_{DRUG} was <5 min, and average, diastolic, intra-arterial pressure at 15 min post-ROSC was approximately 16 mm Hg higher in vasopressin group vs. control ($P = 0.02$). These results imply that the vasoconstricting efficacy of vasopressin may be T_{DRUG}-dependent and that it wares off at $T_{DRUG} > 20$ min. To address this factor of clinical diversity, we conducted an additional subgroup analysis according to "initial rhythm and average $T_{DRUG} < 20$ min for the vasopressin and control groups." This analysis was feasible only at study level and resulted in the exclusion of 2 RCTs[1,25]; in these studies, average T_{DRUG} was approximately 20–21 min in the vasopressin groups and approximately 19–22 min in the control groups. Regarding sustained ROSC in asystole (data available from 2 studies[2,4]), the I^2 value dropped to 0% and results were favourable for vasopressin (vasopressin vs. control, OR = 1.70, 95% CI = 1.17–2.47, $P = 0.005$; Fig. 3C). Regarding long-term survival in asystole (data available from 3 studies[2,4,19]), the I^2 value remained low (i.e. 17%) and results were again favourable for vasopressin (vasopressin vs. control: OR = 2.84, 95% CI = 1.19–6.79, $P = 0.02$; Fig. 3D). In VF/VT and PEA, respective I^2 values ranged within 7–80% and respective results did not reveal any significant vasopressin-related benefit (see eFig. 3 of the eSupplement). Lastly, a heterogeneity test similar to that shown in Fig. 3B yielded a significant I^2 value of 60%, again indicating that the observed differences among the pooled, subgroup ORs for long-term survival are real[21] (Fig. 3E).

3.4. *Sensitivity analysis*

Results were similar to those of our primary analysis and are reported in eSupplement.

4. Discussion

According to overall, pooled results from 4475 adult patients with cardiac arrest, vasopressin with/without epinephrine vs. epinephrine alone during CPR did not improve the rates of sustained ROSC, long-term survival, and long-term survival with CPC score ≤ 2. Nevertheless, the novel finding of the current meta-analysis was that in the large asystole subgroup ($n = 3210$), vasopressin use was associated with an increased probability of long-term survival (absolute % increase–1.0%, corresponding to 10 additional survivors for every 1000 treated patients). Furthermore, the vasopressin-related, survival benefit was quadrupled in an asystole subgroup ($n = 642$) with average $T_{DRUG} < 20$ min (absolute % increase = 4.0%, corresponding to 40 additional survivors for every 1000 treated patients), whereas the corresponding subgroup results on sustained ROSC also favored vasopressin use.

The higher long-term survival in asystole can be attributed mainly to a T_{DRUG}-dependent (i.e. $T_{DRUG} < 20$ min[2,42]) and combined or additional epinephrine-dependent[2,4] vasoconstricting efficacy of the vasopressin-containing regimen during CPR. Indeed, a higher

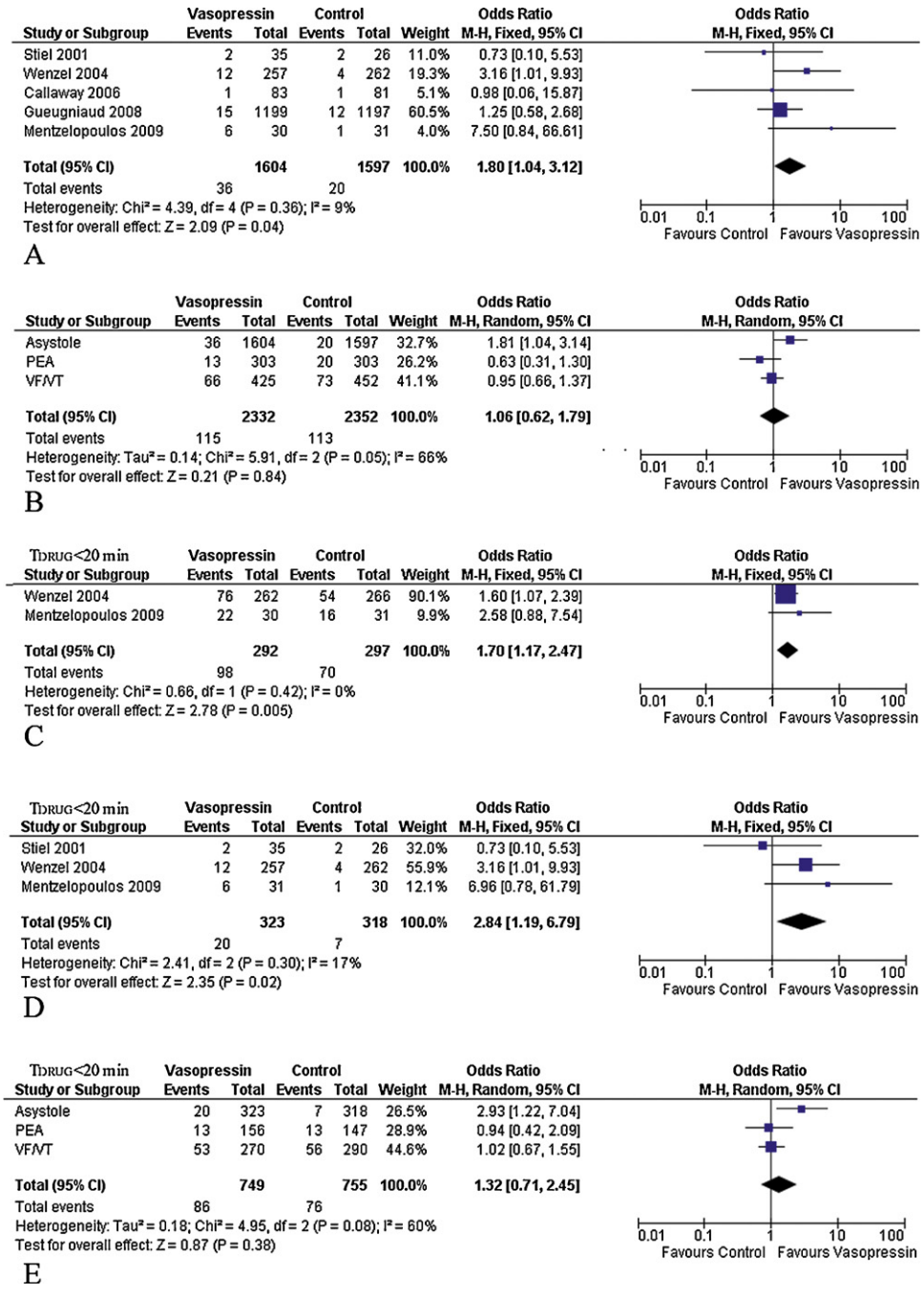

Fig. 3. Main results of the subgroup analyses. (A) Long-term survival in asystole; (B) test for heterogeneity for long-term survival among the initial cardiac rhythm subgroups; the statistically significant I^2 value indicates that the differences in the pooled odds ratios cannot be attributed to chance (see also Section 3); (C) sustained return of spontaneous circulation in the asystole subgroups of studies with average time from cardiovascular collapse to study drug administration (T_{DRUG}) < 20 min; (D) long-term survival in the asystole subgroups of studies with average (T_{DRUG}) < 20 min; (E) test for heterogeneity for long-term survival among the initial cardiac rhythm subgroups of studies with (T_{DRUG}) < 20 min; the statistically significant I^2 value indicates that the differences in the pooled odds ratios cannot be attributed to chance (see also above and Section 3).

diastolic arterial pressure during CPR may accelerate and facilitate ROSC (Fig. 3C), with consequent attenuation of the postresuscitation organ dysfunction, and increased probability of long-term survival.[2] This interpretation is consistent with our subgroup data, which showed that most of the additional asystolic survivors (Fig. 3A and D) received both vasopressors during CPR and originate from studies with average T_{DRUG} < 20 min. In the asystole subgroup of the in-hospital study of Stiell et al.,[19] point estimates for long-term survival did not favor vasopressin (Fig. 3A and D). However, in that study,[19] vasopressin dose was limited to 40 IU, which implies that vasopressin efficacy may also be dose-dependent in asystole.There was no vasopressin-related benefit in VF/VT. This is consistent with the major importance of other, guideline-recommended,[3] ALS interventions (besides vasopressors) in this lethal arrhythmia; examples include amiodarone,[3,30] immediate defibrillation,[3,44] and defibrillation preceded by CPR in prolonged VF/VT.[44–46]

Our subgroup results on PEA were also neutral for vasopressin use (see Section 3 and eSupplement). This supports the hypothesis that in PEA, ROSC and survival may be mainly dependent on the prompt reversal of its causative mechanisms,[3,47–49] rather than enhanced vasoconstriction. For example, severe trauma patients

with out-of-hospital PEA have a dismal prognosis[48,50,51]; in these patients, reversible pathology such as tension haemothorax or pneumothorax, cardiac tamponade, or major haemorrhage may not be promptly treatable before arrival to an emergency department, thus likely reducing the effectiveness of out-of-hospital resuscitative efforts. Also, patients with major ischaemic damage to the left ventricle,[47] even if resuscitated, may be more susceptible to vasopressor-associated, postresuscitation myocardial dysfunction,[7,52,9] which causes a 3.3-fold increase in the probability of subsequent, in-hospital death.[9]

PEA is defined as cardiac electrical activity in the absence of any palpable pulses.[3] However, organized cardiac contractile activity may be present in approximately 40% of PEA patients (pseudo-PEA[48,53]). Pseudo-PEA patients have increased ROSC rates compared to "true PEA" patients,[48,53] and it is unknown whether such patients were balanced between vasopressin and control groups of the included RCTs. In fact, the heterogeneity of our PEA subgroup data might be partly explained by a potentially unequal, between-group distribution of pseudo-PEA in some RCTs. Lastly, the relatively small size of the PEA subgroup ($n = 606$) may have hampered our ability to detect a small difference (e.g. 2–3%; eFig. 2B of the eSupplement) in treatment effect.

Strengths of our meta-analysis include its large sample size ($n = 4475$) and the high methodological quality of the included RCTs. Some limitations are also noteworthy. Overall RCT data exhibited heterogeneity, which was reduced, but not eliminated, in the subgroup analyses. Overall CPC data were missing from 2 studies.[18,25] Subgroup CPC data were missing from 5 studies,[1,4,18,19,25] and the subgroup analysis on neurological outcome was not feasible. Subgroup data on sustained ROSC were also missing from 1 study.[19] We did not specifically address confounders such as differences/variation in witnessed arrest and bystander CPR frequency, times to BLS, ALS, or first shock, frequency of pseudo-PEA, VF/VT protocols following guideline revision (e.g. single-shock vs. three-stacked-shock protocol), ALS duration, vasopressin dose, and quality/intensity of post-ROSC care; the latter also includes therapeutic hypothermia as it was used in just 2 studies[1,2] in non-randomized fashion and use of corticosteroids.[2] Furthermore, our second, study-level, subgroup analysis probably resulted in inclusion of some patients with individual $T_{DRUG} > 20$ min from the 2 included out-of-hospital studies[4,18] and exclusion of some patients with individual $T_{DRUG} < 20$ min from the 2 excluded studies.[1,25]

5. Conclusions

According to the pooled results of 6 RCTs with high methodological quality, vasopressin use in the resuscitation of cardiac arrest patients is not associated with any overall benefit or harm. However, vasopressin may improve the long-term survival of asystolic patients, especially when average T_{DRUG} is <20 min. New RCTs specifically assessing vasopressin effects on subgroup neurological outcome are warranted.

Conflict of interest statement

Dr. Mentzelopoulos has acted as principal investigator and Dr. Zakynthinos as study director in 2 trials (Clinicaltrials.gov identifiers NCT00411879 and NCT00729794). The first trial has been published in the Archives of Internal Medicine and is included in the present meta-analysis and the other trial has been recently completed. Both trials have been funded by the Thorax Research Foundation, Athens, Greece. The first trial has also been funded in part by the Greek Society of Intensive Care Medicine. All funding has been used for the acquisition of disposable materials necessary for the conduct of the aforementioned studies. Dr. Malachias is a co-investigator in NCT00729794. Dr. Wenzel reported the receipt of Grants for the VITRIS at Trauma study. Drs. Siempos and Ulmer do not have any potential conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.resuscitation.2011.07.015.

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