Review

Standard dose epinephrine versus placebo in out of hospital cardiac arrest: A systematic review and meta-analysis☆

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ABSTRACT

Introduction: Out of hospital cardiac arrest (OHCA) is a time critical and heterogeneous presentation. The most appropriate management strategies remain an issue for debate. The aim of this systematic review and meta-analysis was to determine the association of epinephrine versus placebo with return of spontaneous circulation, survival to hospital admission, survival to hospital discharge and neurological outcomes in out of hospital cardiac arrest.

Methods: A systematic review of five databases was performed from inception to August 2018. Only randomised controlled trials were considered eligible for inclusion. The primary outcome was survival to hospital discharge. Secondary outcomes were ROSC, survival to hospital admission, neurological function on discharge and three-month survival. All studies were assessed for level of evidence and risk of bias.

Results: Five randomised controlled trials with 17,635 patients were identified for inclusion. Use of epinephrine was associated with increased ROSC (OR = 3.10; 95% CI = 2.16 to 4.45; I2 = 74%; $p < 0.0001$) and increased survival to hospital admission OR = 2.52; 95% CI = 1.63 to 3.88; I2 = 94%; $p < 0.0001$). However, epinephrine was not associated with increased survival to discharge (OR = 1.09; 95% CI = 0.48 to 2.47; I2 = 77%; $p = 0.84$) or differences in neurological outcomes (OR = 0.81; 95% CI = 0.34 to 1.96).

Discussion: This study was a systematic review and meta-analysis of epinephrine versus placebo in OHCA. The use of epinephrine was associated with improved ROSC and survival to hospital admission. However, use of epinephrine was not associated with a significant difference in survival to hospital discharge, neurological outcomes or survival to 3 months. Further research is required to control for the confounders during inpatient management.

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1. Introduction

Cardiac arrest is the most time critical medical emergency. In out of hospital cardiac arrest (OHCA), immediate bystander cardiopulmonary resuscitation (CPR) and early defibrillation can significantly improve survival [1,2]. Although widely employed, the role of antiarrhythmics in cardiac arrest remains inconclusive and amiodarone and lidocaine, the two most commonly used agents, have failed to show superiority compared to placebo or each other [3].

Epinephrine has been widely used in cardiac arrest since the 1960s with a suggested mechanism of augmenting coronary blood flow by increasing aortic diastolic vascular tone [4]. The use of epinephrine is not without complications, with increased myocardial oxygen consumption, increased arrhythmogenicity and increased myocardial dysfunction [5] after return of spontaneous circulation (ROSC). The myocardial dysfunction seen post ROSC can take the form of simple diastolic dysfunction through to endstage heart failure and death [5]. It also been suggested that epinephrine may reduce cerebral perfusion during CPR [6].

The primary objective of this systematic review and meta-analysis is to study the association of epinephrine versus placebo in OHCA with survival until hospital discharge. The study also aimed to assess

Table 1
Study characteristics.

Study	Sample size (epinephrine/control)	Aetiology of OHCA	Initial cardiac rhythm	Mean Age (yrs)	Volume of trial drug administered (epinephrine/placebo)	OCEBM level of evidence	Risk of bias
Jacobs et al. 2011 [13]	534 (272/262)	>90% presumed cardiac	VF, VT Asystole PEA	65	1 mg in 1 mL epinephrine or 1 mL saline	1b	Low
Nordseth et al. 2012 [14]	174 (101/73)	Not specified	PEA	75	Variable	2b	Moderate
Olasveengen et al. 2011 [15]	858 (367/481)	Not specified	VF/VT, Asystole, PEA	66	Variable	2b	Moderate
Perkins et al. 2018 [16]	8014 (4015/3999)	Medical cause >90%	VF, VT, Asystole, PEA	70	1 mg in 1 mL epinephrine or 1 mL saline	1b	Low
Woodhouse et al. 1995 [17]	245 (145/100)	Not specified	VF, VT, Asystole	68	1 mg in 1 mL epinephrine or 1 mL saline	2b	Severe

Abbreviations: OCEBM - Oxford Centre of Evidence-Based Medicine; VT - pulseless ventricular tachycardia; VF - Ventricular Fibrillation; PEA - Pulseless Electrical Activity; OHCA - Out-of-Hospital Cardiac Arrest.

secondary endpoints including ROSC, survival to admission and survival for longer than 3 months.

2. Methods

2.1. Search strategy

A systematic search was performed by two independent reviewers (LW & CT). The databases searched included MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, SCOPUS and Web of Science from inception to July 2018. The search terms included the medical subject headings "out-of-hospital cardiac arrest", "heart arrest", "ventricular fibrillation" and "epinephrine", with all associated keywords and variations. The search also included ongoing clinical trials (Clinicaltrials.gov, centerwatch.com) and the first 200 results of Google Scholar. No language exclusion criteria were utilised and where required citation titles were translated. For completeness, a manual reference check of included studies was performed and previous meta-analyses were reviewed for any missing publications [7,11,12].

2.2. Eligibility criteria

For a study to be included in this meta-analysis the authors were required to report on (1) adult out of hospital cardiac arrest or cardiopulmonary resuscitation and (2) epinephrine versus placebo. Clinical outcomes of interest were required to be presented. Only randomised controlled trials were eligible for inclusion. Two reviewers (LW & CT) assessed and agreed upon each study for inclusion in this systematic review. Agreement was reached through direct comparison of studies
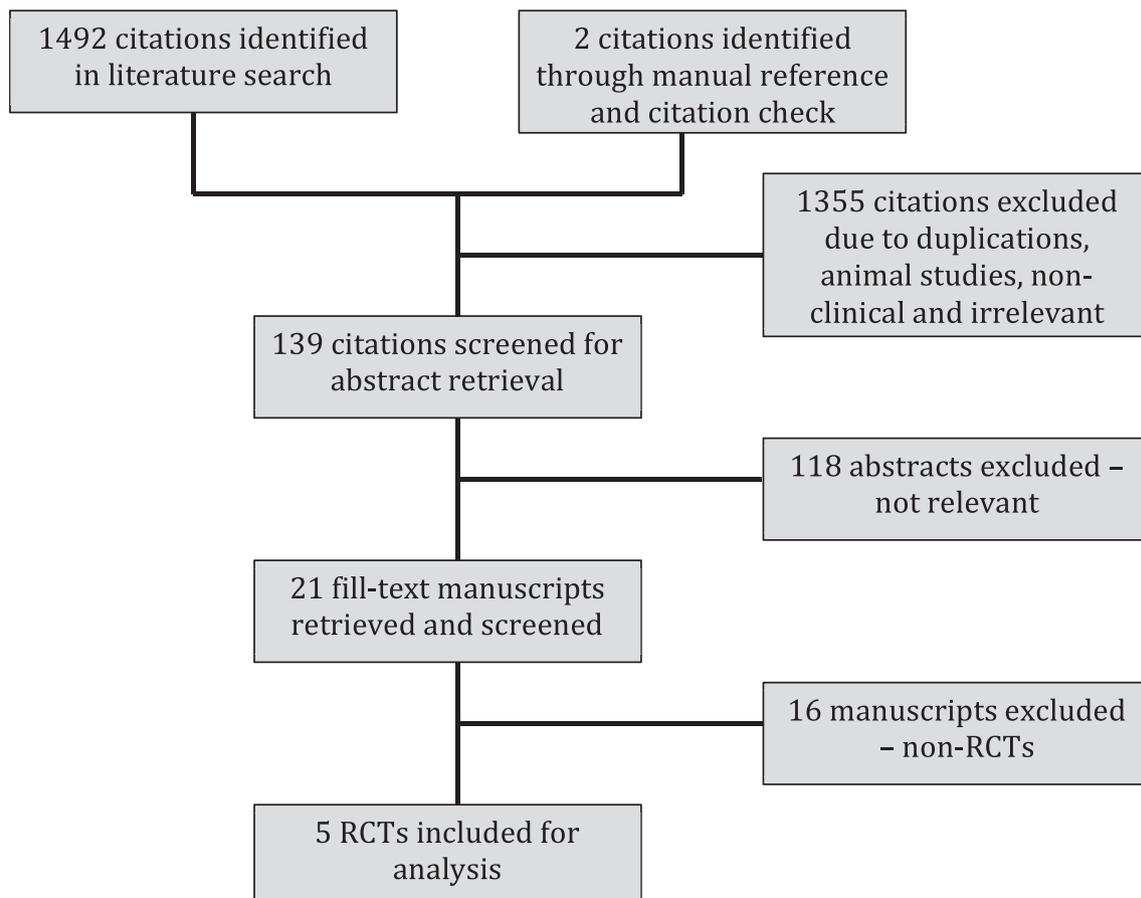
Fig. 1. Flowchart of systematic search.

deemed eligible for inclusion. No instances occurred where a third reviewer was required.

2.3. Exclusion criteria

In-hospital cardiac arrests were not eligible for inclusion. Paediatric and animal studies were also excluded. Studies that compared a combination of epinephrine and another vasopressor versus placebo were excluded, along with any trials which used high dose adrenaline (>1 mg).

2.4. Outcomes

The primary outcome of interest was survival to hospital discharge. Secondary outcomes were ROSC, survival to hospital admission, neurological function on discharge and survival >3 months. Favourable neurological outcomes was defined as moderate or less neurological disability with a Cerebral Performance Category (CPC) score of 1 or 2, or 0 to 3 on the modified Rankin scale.

2.5. Data collection and extraction

Two reviewers (LW and CT) independently extracted data from each article that met the inclusion criteria. The data extracted from each study included patient characteristics, return of spontaneous circulation and survival to hospital discharge. The data collected by each reviewer was then compared for homogeneity.

2.6. Risk of bias

Two independent reviewers assessed each study for risk of bias. Studies were assessed for risk of bias and methodological quality using the Cochrane Collaboration's tool for assessing the risk of bias [8].

2.7. Statistical analyses

The combined data was analysed using RevMan 5.3 software (The Nordic Cochrane Centre, Copenhagen, Denmark) [9]. Dichotomous outcomes were analysed using an Odds Ratio (OR) with 95% confidence

Fig. 2. Summary of the risk of bias in included studies.

interval (CI). The Mantel-Haenszel (M-H) random effects model was used. The absolute difference between the two groups was measured utilizing the risk difference with 95%CIs. Heterogeneity was assess using the I^2 statistic, with an $I^2 > 50\%$ indicating significant heterogeneity. Given we intended to assess four outcome measures, we used the Bonferroni method to minimise the risk of type one errors. Therefore a *p* value of <0.0125 provided evidence of significant OR.

2.8. Subgroup and sensitivity analyses

Where possible, studies were divided into the cardiac rhythm at the time of arrest due to differences in management algorithms for shockable (Ventricular Tachycardia (VT) or Ventricular Fibrillation (VF)) and non-shockable rhythms (Asystole or Pulseless Electrical Activity (PEA)), as well as the likely different aetiologies underlying the cardiac rhythm at the time of arrest.

3. Results

The systematic review of the literature identified five RCTs for inclusion in this meta-analysis [13-17] (Table 1). The initial electronic search identified 1492 studies and a further 2 were identified on manual reference and citation searches. There were no ongoing clinical trials identified. Following the removal of duplicate records and title screening, 139 abstracts were reviewed. Thirty-one full-text manuscripts were reviewed to identify the five included studies. In total data from 17,635 patients were included. A flowchart of the search process is included in Fig. 1. Details of excluded studies are listed in Table S1.

3.1. Risk of bias and level of evidence

Each selected study was assessed for risk of bias and methodological quality using the Cochrane Collaboration's tool for risk of bias (Fig. 2) [8]. Two studies were deemed to be high quality RCTs, one study was found to be of average quality and the remaining two studies were low quality RCTs. Studies were deemed to be low quality if ≥3 bias categories were high risk or undetermined, average quality if 1–2 bias categories were high risk or undetermined, and high quality if investigators had addressed all major bias categories. The level of evidence of the selected studies was determined using the Oxford Centre of Evidence-Based Medicine (OCEBM) levels of evidence.

All five included studies measured ROSC showing a significant improvement with the administration of epinephrine (OR = 3.10; 95% CI = 2.16 to 4.45; I2 = 74%; *p* < 0.0001; Fig. 3). When divided into cardiac rhythm, one study measured VF/VT (OR = 2.36; 95% CI = 1.23 to 4.53; *p* = 0.01; Fig. 3) and two studies measured asystole/PEA (OR = 3.95; 95% CI = 1.47 to 10.59; I2 = 64%; *p* = 0.006; Fig. 3).

Overall, five studies measured survival to admission, showing a significant increase with the administration of epinephrine (OR = 2.52; 95% CI = 1.63 to 3.88; I2 = 84%; *p* < 0.0001; Fig. 4). When separated out into cardiac rhythm there was no significant increase in survival to admission when administered in VF/VT (OR = 1.53; 95% CI = 0.83 to 2.80; I2 = 59%; *p* = 0.17; Fig. 4). The effect of epinephrine remain significant when administered in asystole (OR = 2.97; 95% CI = 1.49 to 5.90; I2 = 77%; *p* = 0.002; Fig. 4).

All five studies measured the effect of epinephrine on survival to discharge, showing no significant effect (OR = 1.09; 95% CI = 0.48 to 2.47; I2 = 77%; *p* = 0.84; Fig. 5). When separated into rhythm for sensitivity analysis, there was no significant effect in VF/VT (OR = 0.74; 95% CI =
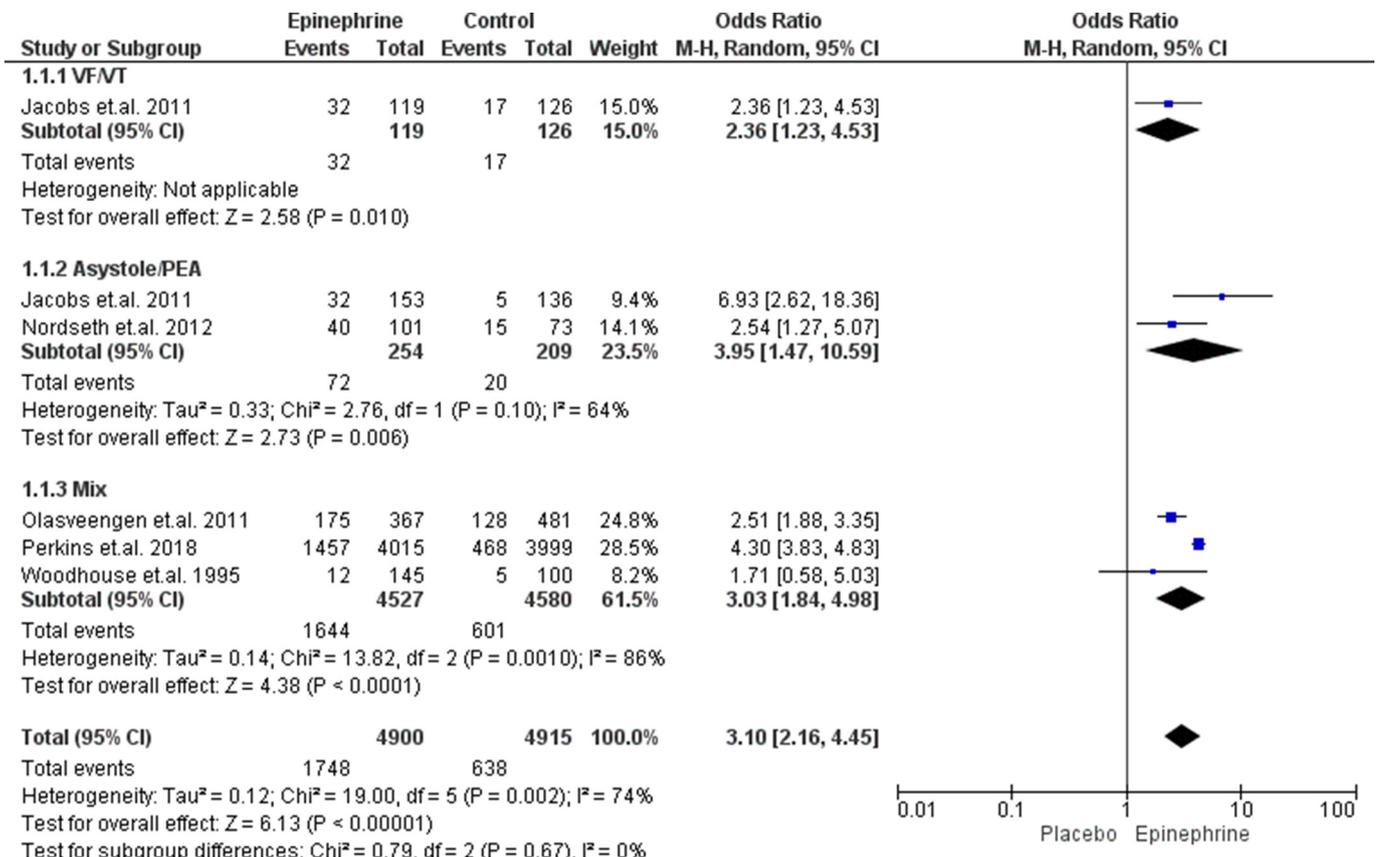

Fig. 3. Return of spontaneous circulation. VF=Ventricular Fibrillation; VT = Ventricular Tachycardia; PEA = Pulseless Electrical Activity.

0.12 to 4.45; I2 = 87%; p = 0.75; Fig. 5) or asystole/PEA (OR = 1.12; 95% CI = 0.19 to 6.65; I2 = 54%; p = 0.90; Fig. 5).

Four of the five studies measured survival to discharge with a good neurological outcome showing no significant difference with the administration of epinephrine (OR = 0.81; 95% CI = 0.34 to 1.96; Fig. 6). One study [15] investigated epinephrine in VF/VT showing significantly worse survival (OR = 0.27; 95% CI = 0.14 to 0.52; p < 0.0001; Fig. 6). This study also showed no effect in asystole/PEA (OR = 0.90; 95% CI = 0.25 to 3.24; p = 0.88; Fig. 6). Neurological outcome was measure in each of these studies by the CPC or modified Rankin scale.

Two studies investigated survival to greater than 3 months. They showed no significant difference (OR = 0.83; 95% CI = 0.27 to 2.48; I2 = 93%; p = 0.73).

4. Discussion

This study was a systematic review and meta-analysis of standard dose epinephrine versus placebo in OHCA cardiac arrest using RCT data. Five RCTs with 17,635 patients were identified for inclusion. Overall, the use of epinephrine was associated with improved ROSC and survival to hospital admission. However, use of epinephrine was not associated with a significant difference in survival to hospital discharge, neurological outcomes or survival to 3 months.

The proposed mechanism of epinephrine augmenting coronary blood flow by increasing aortic vasomotor tone appears to be supported by this study, as use of epinephrine was associated with both increased ROSC (OR = 3.10; 95% CI = 2.16 to 4.45; I2 = 74%; p < 0.0001) and increased survival to hospital admission (OR = 2.52; 95% CI = 1.63 to 3.88; I2 = 94%; p < 0.0001). The high degree of heterogeneity is likely the result of cardiac arrest being an entity with a wide variety of aetiologies and variable early management. This meta-analysis was unable to account for confounders such as duration and quality of CPR, usage and cumulative dosage of antiarrhythmics, airway management strategies, experience of care providers and confirmed causes of arrest, all of which contribute to survival and neurological outcome.

The association of epinephrine with improved post-OHCA outcomes appears lost once inpatient management is commenced. Epinephrine was not associated with increased survival to discharge (OR = 1.09; 95% CI = 0.48 to 2.47; I2 = 77%; p = 0.84) or differences in neurological outcomes (OR = 0.81; 95% CI = 0.34 to 1.96). One study investigated neurological outcomes at time of hospital discharge using epinephrine in VF/VT, which showed significantly worse survival (OR = 0.27; 95% CI = 0.14 to 0.52; p < 0.0001). The studies included in this meta-analysis did not control for post-arrest care and as such these outcomes are difficult to interpret.

The primary endpoint in this study was survival to discharge. Most secondary endpoints including ROSC, survival to admission and survival for longer than 3 months were equally easily defined and measured as the primary outcome. Neurological outcome at discharge is a more subjective endpoint. Different neurological assessment scores were used in the trials included in this analysis. Although the Modified Rankin Score and the CPC Score both aim to correlate neurological outcome and degree of disability, the discrete numbering system provides a crude measure of the subtle neurological disability that can occur post cardiac arrest. Application of the score is also reviewer dependent, resulting in concerns about variability in neurological assessment outcomes [18,19]. Of additional consequence is the concept of survivor bias. This subtype of selection bias, in which only those patients who survive to discharge can be assessed for neurological outcomes, may produce a skewed view of neurological outcomes post cardiac arrest. Should management of OHCA become more efficacious and increase survival to discharge, there may be both a statistical and clinically apparent deterioration in neurological outcomes as patients with longer periods of cerebral hypoxia survive to discharge.
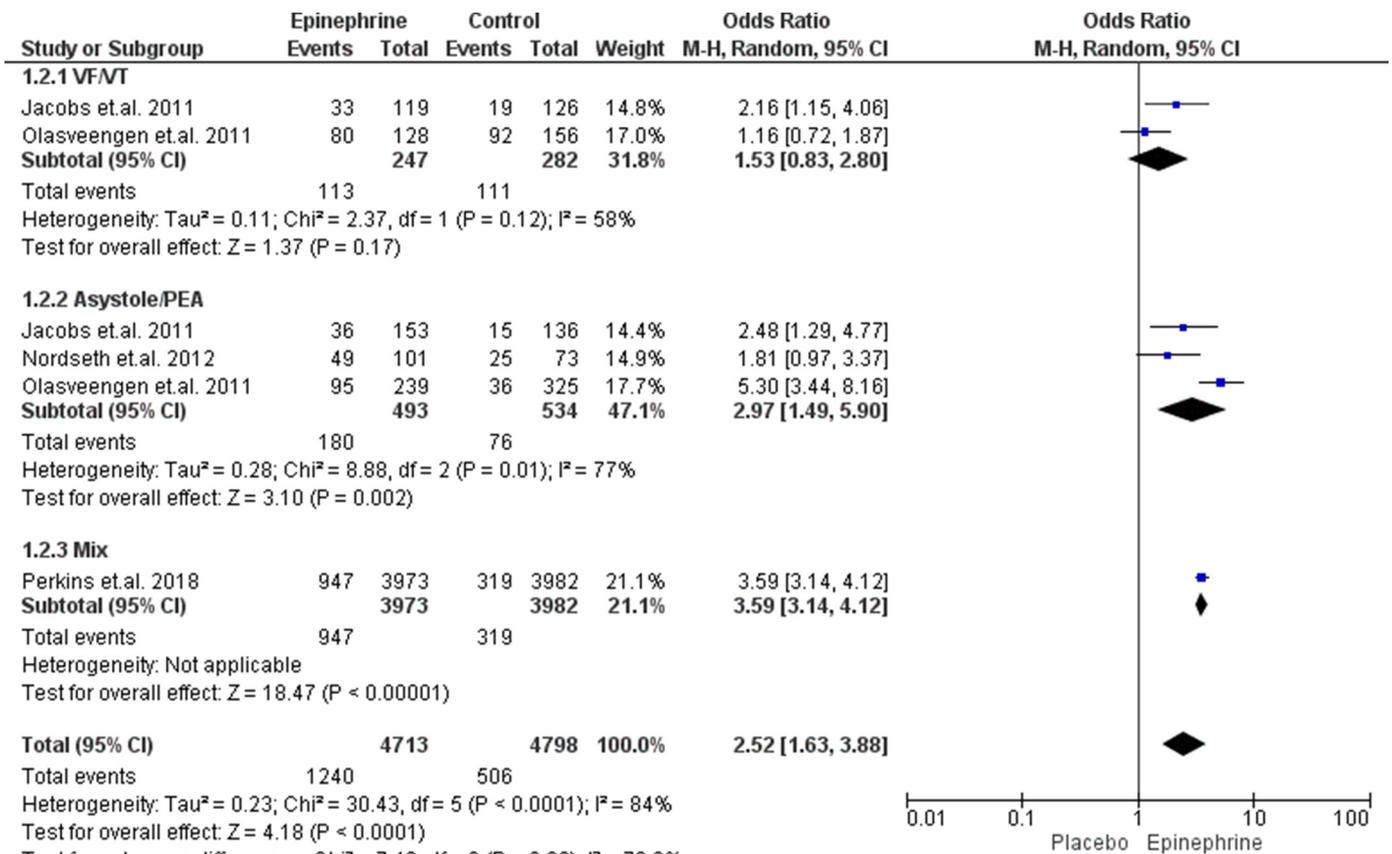
Study or Subgroup	Epinephrine Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 VF/VT						
Jacobs et.al. 2011	33	119	19	126	14.8%	2.16 [1.15, 4.06]
Olasveengen et.al. 2011	80	128	92	156	17.0%	1.16 [0.72, 1.87]
Subtotal (95% CI)		247		282	31.8%	1.53 [0.83, 2.80]
Total events	113		111			
Heterogeneity: Tau² = 0.11; Chi² = 2.37, df = 1 (P = 0.12); I² = 58%						
Test for overall effect: Z = 1.37 (P = 0.17)						
1.2.2 Asystole/PEA						
Jacobs et.al. 2011	36	153	15	136	14.4%	2.48 [1.29, 4.77]
Nordseth et.al. 2012	49	101	25	73	14.9%	1.81 [0.97, 3.37]
Olasveengen et.al. 2011	95	239	36	325	17.7%	5.30 [3.44, 8.16]
Subtotal (95% CI)		493		534	47.1%	2.97 [1.49, 5.90]
Total events	180		76			
Heterogeneity: Tau² = 0.28; Chi² = 8.88, df = 2 (P = 0.01); I² = 77%						
Test for overall effect: Z = 3.10 (P = 0.002)						
1.2.3 Mix						
Perkins et.al. 2018	947	3973	319	3982	21.1%	3.59 [3.14, 4.12]
Subtotal (95% CI)		3973		3982	21.1%	3.59 [3.14, 4.12]
Total events	947		319			
Heterogeneity: Not applicable						
Test for overall effect: Z = 18.47 (P < 0.00001)						
Total (95% CI)		4713		4798	100.0%	2.52 [1.63, 3.88]
Total events	1240		506			
Heterogeneity: Tau² = 0.23; Chi² = 30.43, df = 5 (P < 0.0001); I² = 84%						
Test for overall effect: Z = 4.18 (P < 0.0001)						
Test for subgroup differences: Chi² = 7.46, df = 2 (P = 0.02), I² = 73.2%						

Fig. 4. Survival to admission. VF = Ventricular Fibrillation; VT = Ventricular Tachycardia; PEA = Pulseless Electrical Activity.

Neurological outcome is therefore an important endpoint, as post-arrest function is integral to the aims of management, that is to maintain life but also prevent disability. As such post arrest neuroprotective strategies have also become an important topic of research in peri-arrest management. Although the present trials did not discuss post arrest neuroprotective strategies, four of the five did measure neurological outcome at discharge. The mainstay of neuroprotection post cardiac arrest is the implementation of mild hypothermia once cerebral perfusion is achieved, resulting in a significantly higher neurological recovery (the ability to live independently and work at least part time) than those patients who maintain normothermia [20]. Future studies following the outcomes of OHCA would benefit from attention to post arrest neurological management, and subsequent assessment of neurological outcome based on consistent assessment and scoring.

Studies of in hospital cardiac arrest (IHCA) were excluded from this analysis on the basis that timing of arrest management, including time to first administration of epinephrine is likely to be shorter in hospital where a specialised arrest team is available. Although the effects of time to first epinephrine administration were not examined in these studies, later administration has been demonstrated to result in both reduced survival and poorer neurological outcome for OHCA [21]. In the PARAMEDIC2 Trial published earlier this year, epinephrine was administered an average of 21 min post emergency call [16]. The response time should be more prompt in the inpatient setting, meaning that the results of this analysis are not applicable to IHCA.

This analysis produced significant heterogeneity for both the primary, as well as the secondary outcomes. As discussed above while this may be due to variation in the aetiology and early management of OHCA, contributing to this is the relatively low number of RCTs, especially in the subgroup analyses, and the variable quality of these studies (Fig. 2). Specific variations in management that will contribute to

heterogeneity include the duration and quality of CPR, which is in turn influenced by the place and timing of the arrest, and therefore also the experience of the providers.

Variation in local protocols due to location and time is another confounder in this study. The trials included in this analysis originated in the United Kingdom, Norway and Australia, and variations in protocols, as well as service availability and efficiency will vary between countries and health care sites. Additionally the publication dates of the trials range from 1995 to 2018 (although four of the studies have been published since 2011), over which time there have been changes in protocols based on emerging evidence on the management of OHCA.

Along the same theme, there was no control for administration of other agents such as amiodarone or lignocaine or for airway management, which may also vary depending on operator experience and local protocols. Finally, the studies poorly described the total number of adrenaline doses given which may negatively influence the post arrest outcomes in certain studies.

Based on the above limitations, recommendations for future studies would include attention to the dosing of epinephrine, as well as either protocolisation or documentation of other confounders such as airway management strategies and drug administration for subgroup analysis.

While demonstrating a significant return in ROSC and survival to hospital admission, the analysis does not support the use of epinephrine for the outcomes of survival to discharge, favourable neurological outcome, and 3-month survival. Some benefit may be obtained however from increasing survival to hospital admission in terms of increasing the pool of potential organ donors. This is a complex ethical issue that warrants further discussion. The present results suggest that while epinephrine plays an important role in the initial management of OHCA, the benefit is lost at the point of implementation of hospital management. That considered the high degree of heterogeneity between the
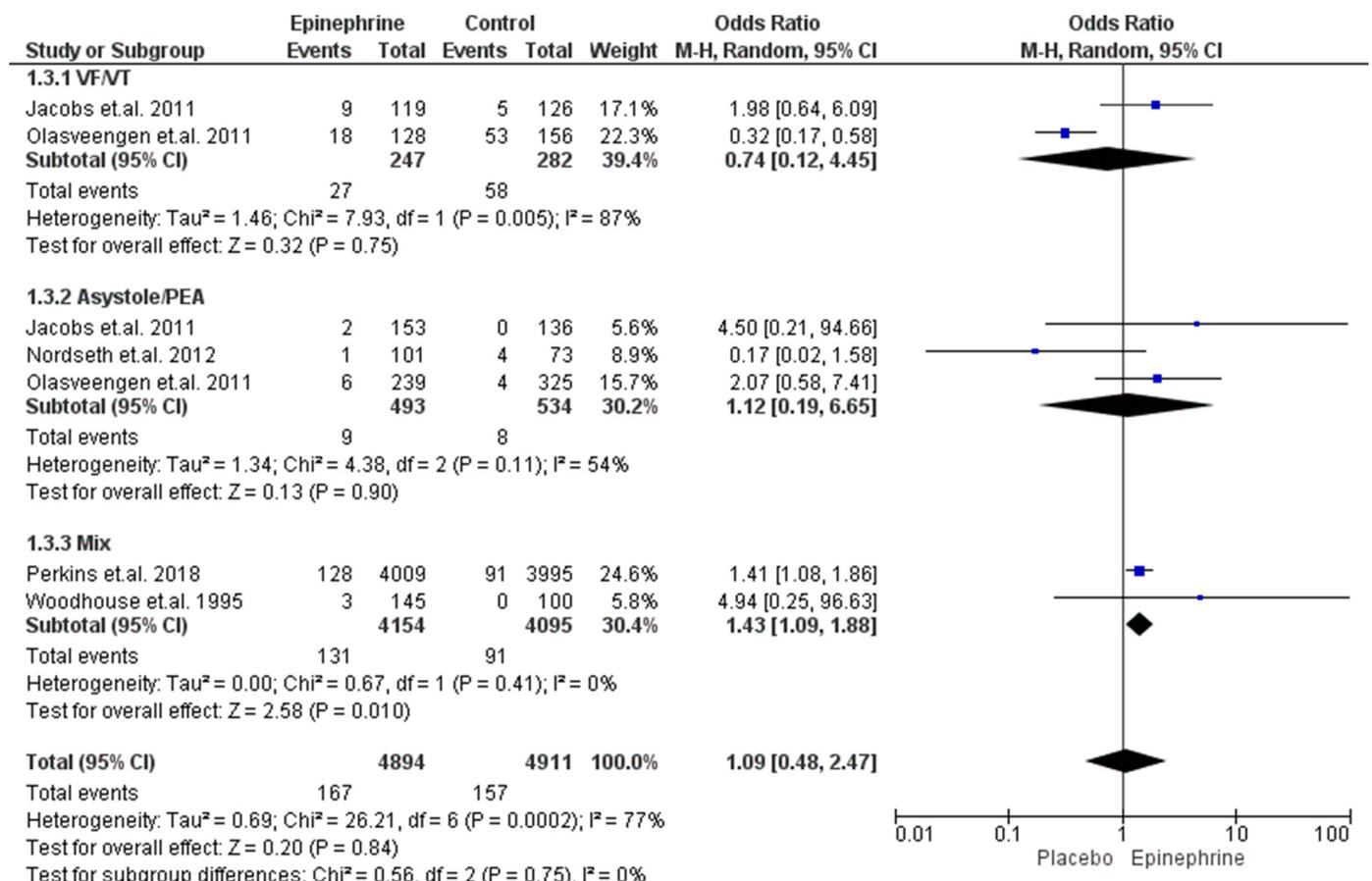

Fig. 5. Survival to discharge. VF = Ventricular Fibrillation; VT = Ventricular Tachycardia; PEA = Pulseless Electrical Activity.
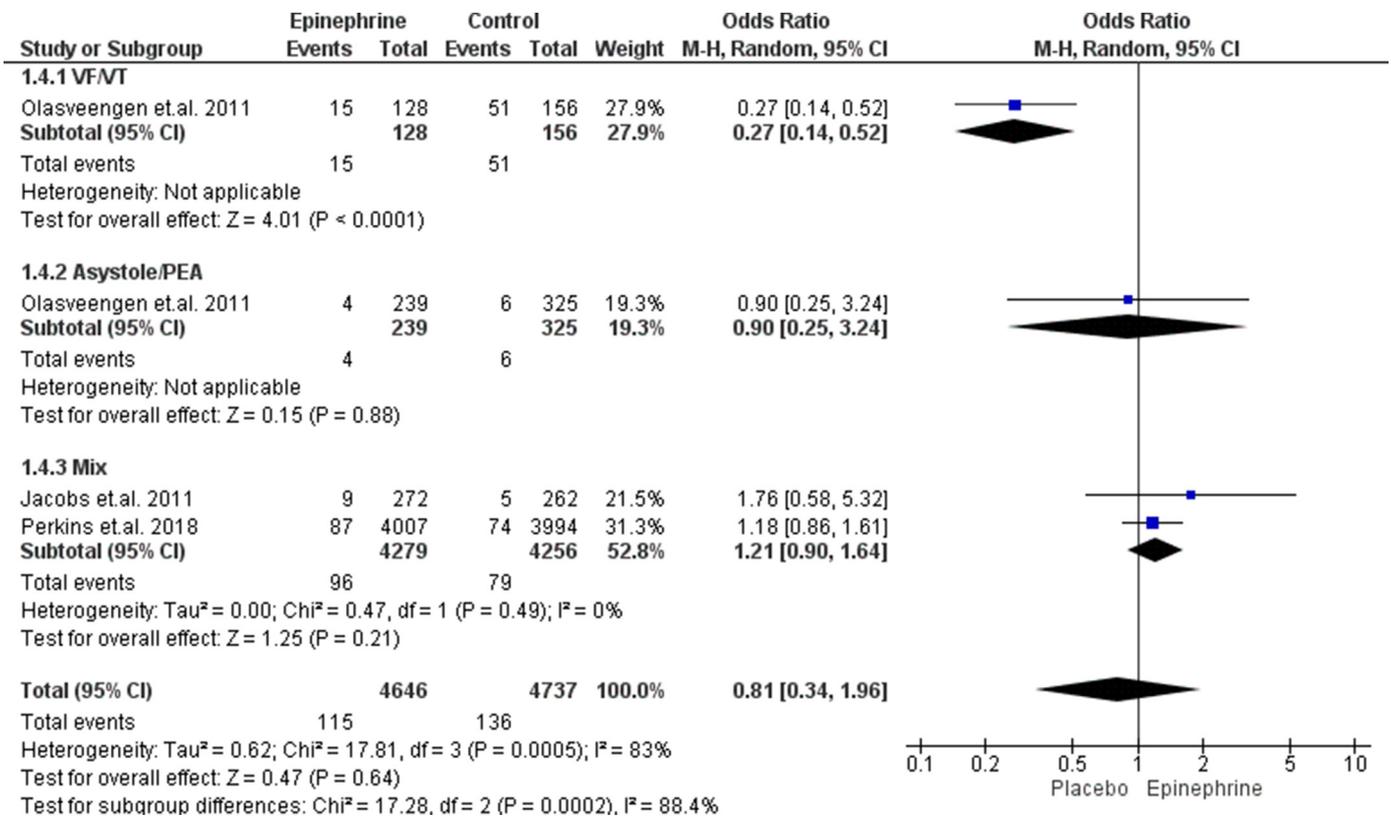
Fig. 6. Neurological outcome. VF = Ventricular Fibrillation; VT = Ventricular Tachycardia; PEA = Pulseless Electrical Activity.

present studies would support further trials with greater attention to specifics of peri-arrest management such as timing and cumulative dose of epinephrine, as well as post arrest neuroprotection, and other hospital management protocols and techniques. This will better define the role for epinephrine the management of out of hospital cardiac arrest and highlight elements of post arrest management that can be improved to retain the initial benefits observed in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2018.12.055.

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