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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	8
Figure 1.	9
Figure 2.	11
Figure 3.	12
DISCUSSION	14
AUTHORS' CONCLUSIONS	15
ACKNOWLEDGEMENTS	16
REFERENCES	17
CHARACTERISTICS OF STUDIES	19
DATA AND ANALYSES	24
Analysis 1.1. Comparison 1 CPR plus delayed defibrillation versus immediate defibrillation, Outcome 1 Survival to hospital discharge.	25
Analysis 1.2. Comparison 1 CPR plus delayed defibrillation versus immediate defibrillation, Outcome 2 Good neurological recovery at hospital discharge.	26
Analysis 1.3. Comparison 1 CPR plus delayed defibrillation versus immediate defibrillation, Outcome 3 ROSC.	27
Analysis 1.4. Comparison 1 CPR plus delayed defibrillation versus immediate defibrillation, Outcome 4 Survival at 1 year.	27
Analysis 2.1. Comparison 2 Sensitivity analysis: does the methodological quality influence the effects?, Outcome 1 Survival to hospital discharge (studies with low risk of bias).	28
Analysis 2.2. Comparison 2 Sensitivity analysis: does the methodological quality influence the effects?, Outcome 2 ROSC (studies with low risk of bias).	29
Analysis 2.3. Comparison 2 Sensitivity analysis: does the methodological quality influence the effects?, Outcome 3 Survival at 1 year (studies with low risk of bias).	29
APPENDICES	29
WHAT'S NEW	34
HISTORY	34
CONTRIBUTIONS OF AUTHORS	34
DECLARATIONS OF INTEREST	34
SOURCES OF SUPPORT	35
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	35
INDEX TERMS	35

[Intervention Review]

Cardiopulmonary resuscitation (CPR) plus delayed defibrillation versus immediate defibrillation for out-of-hospital cardiac arrest

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ABSTRACT

Background

Sudden cardiac arrest (SCA) is a common health problem associated with high levels of mortality. Cardiac arrest is caused by three groups of dysrhythmias: ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), pulseless electric activity (PEA) and asystole. The most common dysrhythmia found in out-of-hospital cardiac arrest (OHCA) is VF. During VF or VT, cardiopulmonary resuscitation (CPR) provides perfusion and oxygenation to the tissues, whilst defibrillation restores a viable cardiac rhythm. Early successful defibrillation is known to improve outcomes in VF/VT. However, it has been hypothesized that a period of CPR before defibrillation creates a more conducive physiological environment, increasing the likelihood of successful defibrillation. The order of priority of CPR versus defibrillation therefore remains in contention. As previous studies have remained inconclusive, we conducted a systematic review of available evidence in an attempt to draw conclusions on whether CPR plus delayed defibrillation or immediate defibrillation resulted in better outcomes in OHCA.

Objectives

To examine whether an initial one and one-half to three minutes of CPR administered by paramedics before defibrillation versus immediate defibrillation on arrival influenced survival rates, neurological outcomes or rates of return of spontaneous circulation (ROSC) in OHCA.

Search methods

We searched the following databases: the Cochrane Central Register of Controlled trials (CENTRAL) (2013, Issue 6); MEDLINE (Ovid) (1948 to May 2013); EMBASE (1980 to May 2013); the Institute for Scientific Information (ISI) Web of Science (1980 to May 2013) and the China Academic Journal Network Publishing Database (China National Knowledge Infrastructure (CNKI), 1980 to May 2013). We included studies published in all languages. We also searched the Current Controlled Trials and Clinical Trials databases for ongoing trials. We screened the references lists of studies included in our review against the reference lists of relevant International Liaison Committee on Resuscitation (ILCOR) evidence worksheets.

Selection criteria

Our participant group consisted of adults over 18 years of age presenting with OHCA who were in VF or pulseless VT at the time of emergency medical service (EMS) paramedic arrival. We included randomized controlled trials (RCTs) and quasi-randomized controlled trials that evaluated the effects of one and one-half to three minutes of CPR versus defibrillation as initial therapy on survival and neurological outcomes of these participants. We excluded observational and cross-over design studies.

Data collection and analysis

Two review authors independently extracted the data. We contacted study authors to ask for additional data when required. The risk ratio (RR) for each outcome was calculated and summarized in the meta-analysis after heterogeneity was considered. We used Review Manager software for all analyses.

Main results

We included four RCTs with a total of 3090 enrolled participants (one study used a cluster-randomized design). Three trials were considered to have a relatively low risk of bias, and one trial was considered to have a relatively high risk. When survival to hospital discharge was compared, 38 of 320 (11.88%) participants survived to discharge in the initial CPR plus delayed defibrillation group compared with 39 of 338 participants (11.54%) in the immediate defibrillation group (RR 1.09, 95% CI 0.54 to 2.20, $\chi^2 = 10.78$, degrees of freedom (df) = 5, P value 0.06, $I^2 = 54\%$, low-quality evidence).

When we compared the neurological outcome at hospital discharge (RR 1.12, 95% CI 0.65 to 1.93, low-quality evidence), the rate of return of spontaneous circulation (ROSC) (RR 0.94, 95% CI 0.77 to 1.15, low-quality evidence) and survival at one year (RR 0.77, 95% CI 0.24 to 2.49, low-quality evidence), we could not rule out the superiority of either treatment.

Adverse effects were not associated with either treatment.

Authors' conclusions

Owing to the low quality of available evidence, we have been unable to determine conclusively whether immediate defibrillation and one and one-half to three minutes of CPR as initial therapy before defibrillation have similar effects on rates of return of spontaneous circulation, survival to discharge or neurological insult.

We have also been unable to conclude whether either treatment approach provides a degree of superiority in OHCA.

We propose that this is an area that needs further rigorous research through additional high-quality RCTs, including larger sample sizes and proper subgroup analysis.

PLAIN LANGUAGE SUMMARY

Should health care providers arriving at scene of a cardiac arrest give a period of chest compressions first before providing a rapid electric shock

Out-of-hospital cardiac arrest (OHCA) is a major cause of death worldwide. Cardiac arrest occurs when the rhythm of the heart becomes disorganized and the heart becomes ineffective at pumping blood to the rest of the body. Prolonged periods of reduced oxygen to the brain can cause permanent damage. Cardiac arrest can be caused by, but is different from, a heart attack (myocardial infarction).

The disorganized rhythm that the heart goes into in cardiac arrest is often amenable to electric shock therapy (defibrillation). Chest compressions are also very important, as they go some way toward replicating the heart's action by pumping oxygen-rich blood through the body, rescuing the organs by providing them with oxygen and nutrients. Some scientists have proposed that it is better for health care providers to give a period of chest compressions before providing an electric shock to restart the heart, rather than giving an immediate electric shock, when they arrive on the scene. The idea is that chest compressions make the electric shock more likely to be successful, as the chest compressions start to rescue conditions within the body, making it a more conducive environment for a normal heart rhythm to establish itself after defibrillation. We decided to investigate this question by conducting a Cochrane systematic review to assess whether any evidence from trials would support this theory. We searched available databases until May 2013 to find suitable trials for review, and we included four randomized controlled trials with a total number of 3090 patients.

After reviewing the studies and their available data, we could not be certain that one approach had superiority over another, and we could not establish whether the two treatments had similar effects on outcomes. We found no adverse effects associated with either treatment. Currently, no definitive evidence allows us to conclude that chest compressions should be the initial therapy for patients with OHCA over immediate electric shock treatment. However, we believe that the amount and quality of research in this area currently are not sufficient to allow strong conclusions. To further our understanding of the efficacy of these two different strategies, further rigorous randomized controlled trials are required.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. CPR plus delayed defibrillation versus immediate defibrillation: overall analysis

Overall analysis

Patient or population: patients with out-of-hospital cardiac arrest
Settings: urban areas in four different countries (Norway, Australia, United States and Canada)
Intervention: cardiopulmonary resuscitation plus delayed defibrillation
Comparison: immediate defibrillation

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Immediate defibrillation	Cardiopulmonary resuscitation plus delayed defibrillation				
Survival to hospital discharge rate	115 per 1000	126 per 1000 (62 to 254)	RR 1.09 (0.54 to 2.2)	658 (3 studies)	⊕⊕⊕⊖ low ^{a,b,c}	
Neurological outcome at hospital discharge rate of good recovery	185 per 1000	207 per 1000 (120 to 357)	RR 1.12 (0.65 to 1.93)	2834 (3 studies)	⊕⊕⊕⊖ low ^{b,c,d}	
ROSC rate	328 per 1000	309 per 1000 (253 to 378)	RR 0.94 (0.77 to 1.15)	658 (3 studies)	⊕⊕⊕⊖ low ^{a,b,c}	
Survival at 1 year rate Follow-up: median 1 year	90 per 1000	69 per 1000 (22 to 224)	RR 0.77 (0.24 to 2.49)	456 (2 studies)	⊕⊕⊕⊖ low ^{a,b,c}	

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ^aOne trial used a quasi-randomized design, and no information on random sequence generation was provided in all trials.
- ^bRandomized design according to the text, but no information on random sequence generation was provided in the 2 trials.
- ^c95% confidential intervals range a lot.
- ^d95% confidential intervals of RR in the 2 groups are poorly overlapped

BACKGROUND

Description of the condition

Sudden cardiac arrest (SCA) is a common public health problem that occurs worldwide. Approximately 350,000 people per year suffer a cardiac arrest in North America (Chan 2010; Jones 2007; Nadkarni 2006; Nichol 2008). Cardiac arrest occurs mainly in adults; however the incidence of paediatric out-of-hospital cardiac arrest (OHCA) in North America is approximately eight in 100,000 persons per year (Atkins 2009). Cardiac arrest is generally caused by three rhythms: ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), pulseless electric activity (PEA) and asystole. The rhythm found most frequently in OHCA is VF (Valenzuela 1997). The survival rate from OHCA remains poor (Kern 1990) for all patients (including adults and infants). Clinical trials have found the survival rate to be between 1% and 11% or even lower (Dunne 2007; Vaillancourt 2008). Clinical data have shown that in a witnessed SCA, however, survival of almost 50% has been reported when the links in the 'chain of survival' have been effectively executed by the emergency medical service (Agarwal 2009; Chan 2010; Hinchey 2010). Improvements in treatment of SCA may save thousands of lives.

Description of the intervention

Defibrillation is defined as termination of VF for at least five seconds following delivery of an electric shock by a defibrillator (Link 2010). The electrical energy delivered to the heart can reestablish a normal cardiac rhythm and in turn sufficient cardiac output to perfuse the tissues. The recommended energy dose for biphasic defibrillators is 120 to 200 joules (J) (Martens 2001; Stiell 2007). Defibrillation is the fundamental therapy used to stop VF, leading to cardioversion and the return of spontaneous circulation (ROSC). Cardiopulmonary resuscitation (CPR) comprises chest compression and artificial respiration. CPR, especially chest compression, is essential for maintaining the perfusion and oxygen supply to vital organs when pulseless rhythms (including VF and pulseless VT) occur. This improves the patient's chances of survival and prolongs the window of opportunity for defibrillation (Iwami 2007; Larsen 1993; Ong 2008; SOS-KANTO Study Group 2007).

How the intervention might work

When a person collapses from SCA, he or she suffers a period of profound global ischaemia. The tolerance of our tissues to hypoxia is limited, and hypoxia will lead to irreversible neurological damage if untreated VF lasts longer than several minutes. If no CPR is provided after collapse because of VF, the survival rate will decrease by 7% to 10% for each additional minute between collapse and defibrillation (Larsen 1993). Chest compressions work by increasing intrathoracic pressure and by mechanically pumping the heart to create cardiac output. Artificial ventilation helps to maintain oxygenation and eliminate carbon dioxide (CO₂); therefore, CPR provides crucial perfusion and delivery of oxygen to the tissues (Berg 2010; Jonas 2006).

Basic CPR (including chest compression and artificial ventilation) is unlikely to stop VF (Valenzuela 1997). Therefore we need defibrillation to restore a perfusing rhythm. We use a defibrillator to create a current that flows across the heart, producing synchronized depolarization of the cardiac myocytes, which pauses VF and allows cardiac pacemaker cells to establish a

normal cardiac rhythm. In the 2010 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC), the following were considered to be the first three links in the 'chain of survival': immediate recognition, early CPR and rapid defibrillation (Berg 2010). These three links are considered to be essential in improving rates of ROSC and survival and neurological outcomes (Rea 2006).

Clinical trials have shown that shorter times from collapse to CPR and from collapse to defibrillation in an episode of VF are associated with better outcomes. Rapid integration of CPR and defibrillation is thought to be important and beneficial. According to the AHA guidelines for CPR and ECC, if an automated external defibrillator (AED) is available, the rescuer should use it as quickly as possible after witnessing an OHCA. In situations where other bystanders or rescuers are at hand, high-quality CPR should be delivered as early as possible while others are alerting emergency medical services (EMS), retrieving an AED and preparing for defibrillation (Berg 2010). However, when untreated VF has lasted longer than three to five minutes (i.e. the individual has received no treatment), previous research suggests that a period of chest compression before defibrillation may be beneficial (Stiell 2008) because after a few minutes of untreated VF, depletion of oxygen and metabolic substrates will occur, leading to worsened cardiac electrophysiological function and a hypothesized decreased chance of successful defibrillation.

The patient's electrical and mechanical cardiac function will deteriorate as untreated VF continues (Kern 1990). A period of CPR (one and one-half to three minutes is recommended in most cases) may partially reverse these changes and deliver oxygen and energy substrates (Eftestol 2004), thereby increasing the probability of successful defibrillation (as the physiological milieu is improved for the myocytes). Randomized controlled trials (RCTs) and cohort studies have suggested that a period of CPR before defibrillation would increase the rate of ROSC and survival to hospital discharge when ambulance or EMS response intervals are four to five minutes or longer; no differences between the two treatments have been noted with ambulance response times shorter than five minutes (Cobb 1999; Wik 2003). However, some studies suggest that a period of initial CPR before defibrillation may not provide any benefit for ROSC and survival to hospital discharge rates (Baker 2008; Bradley 2010; Hayakawa 2009; Jacobs 2005). Therefore in an OHCA not witnessed by EMS, current evidence is unclear regarding whether a period of CPR before defibrillation may be more beneficial than immediate defibrillation. In 2010, the AHA Guidelines for CPR and ECC recommended that EMS rescuers should begin CPR while others are checking electrocardiographic (ECG) rhythm and preparing for a shock (Berg 2010).

Why it is important to do this review

Although the 2010 AHA Guidelines for CPR and ECC have provided the recommendations presented above (Berg 2010), whether it is effective or beneficial for professional rescuers to delay rhythm analysis and defibrillation to provide CPR for one and one-half to three minutes remains a critical question for OHCA not witnessed by EMS (Link 2010). As has been described, clinical trials that address this question (including RCTs and observational studies) have resulted in variable conclusions. Some results have suggested that a period of CPR before rhythm analysis and defibrillation was beneficial for the outcome of OHCA, but others have not shown this to be the case. The effects of the two strategies on survival from

OHCA and on other outcomes such as neurological function remain unclear (Cobb 1999; Hayakawa 2009; Jacobs 2005; Wik 2003). To date, no systematic reviews have evaluated the findings of RCTs on this topic. We propose that a Cochrane systematic review of RCTs may reveal the different effects of the two strategies on the outcomes of patients who have collapsed from OHCA. We propose that this review may also provide an answer as to the priority of initial CPR and defibrillation, allowing us to provide further recommendations on how treatment of SCA can be improved.

OBJECTIVES

To examine whether an initial one and one-half to three minutes of CPR administered by paramedics before defibrillation versus immediate defibrillation on arrival influenced survival rates, neurological outcomes or rates of ROSC in OHCA.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized and quasi-randomized controlled trials that evaluated the effects of one and one-half to three minutes of CPR as first therapy versus defibrillation as first therapy on survival and neurological outcomes of out-of-hospital cardiac arrest.

We excluded cohort studies and studies using a cross-over design.

Types of participants

We included participants with OHCA who presented with VF or pulseless VT at the time of arrival of EMS paramedics. Cardiac arrest was defined as an inability to find cardiac mechanical activity or a pulse. The rhythm was confirmed by an AED or an electrocardiograph (ECG) after the arrival of EMS rescuers.

We excluded children and adolescents (i.e. those younger than 18 years of age).

We excluded OHCA caused by trauma or drowning because of the different physiology and prognosis associated with this event.

Types of interventions

After the arrival of EMS personnel, the rescuer should prepare to check the ECG and apply a defibrillator immediately, while other rescuers simultaneously perform chest compression and ventilation with advanced airway, without disturbing preparations for the ECG or defibrillator.

We considered study participants who received one and one-half to three minutes of high-quality CPR (including chest compression and ventilation with advanced airway) before the first defibrillation as constituting the intervention group.

We considered participants for whom defibrillation was administered immediately after the defibrillator was applied as the control group.

Except for CPR time before the first defibrillation, other treatments provided to the two groups were the same, and cardiac arrest was managed in accordance with relevant guidelines.

Types of outcome measures

Primary outcomes

1. Survival to hospital discharge.

Secondary outcomes

1. Neurological outcomes at hospital discharge, assessed by cerebral performance category (CPC) or other validated scales with equivalent effect. These important outcomes are used to evaluate the quality of life after successful CPR. Neurological outcomes at hospital discharge measured as CPC were grouped into two categories: good recovery (defined as a CPC score of 1 or 2) and unfavourable recovery (defined as a CPC score of 3, 4 or 5).
2. Rate of return of spontaneous circulation (ROSC).
3. Survival at one year.

Search methods for identification of studies

Electronic searches

We searched the following databases: the Cochrane Central Register of Controlled trials (CENTRAL) (2013, Issue 6; see [Appendix 1](#)); MEDLINE (Ovid SP, 1948 to May 2013; see [Appendix 2](#)); EMBASE (Ovid SP, 1980 to May 2013; see [Appendix 3](#)) and Institute for Scientific Information (ISI) Web of Science (1980 to May 2013; see [Appendix 4](#)). We also searched the following Chinese database: China Academic Journal Network Publishing Database (1980 to May 2013; see [Appendix 5](#)). The search of MEDLINE and EMBASE included the high-sensitivity search strategies for randomized controlled trials described by Higgins et al ([Higgins 2011](#)).

We included studies published in any language.

Searching other resources

We searched the following databases for ongoing trials: <http://www.controlled-trials.com> and <http://clinicaltrials.gov>.

We screened the reference lists of all studies included in our review, as well as the reference lists of relevant International Liaison Committee on Resuscitation (ILCOR) evidence worksheets (<http://www.ilcor.org/>).

Data collection and analysis

Selection of studies

We combined the results of the searches described above and excluded duplicate studies. Two review authors (LY and YH) independently screened all titles and abstracts for eligibility (see [Appendix 6](#); [Appendix 7](#)). If any doubt remained as to whether a title or abstract should be included or excluded from the review, we read the full text before making a decision. We resolved disagreements by discussion with a third review author (QH).

We planned to contact the authors of relevant articles if further information was required to make a decision about trial inclusion.

We recorded all eligible trials on a trials form (see [Appendix 8](#)).

Data extraction and management

Two authors (YH and LY) independently extracted and collected data and recorded this information on data extraction forms (copies

of these forms can be found in [Appendix 9](#) to [Appendix 11](#)). We resolved discrepancies through discussion and involved a third review author (QH) when we were unable to reach a consensus.

We planned to contact the authors of clinical trials to ask for more information, if necessary.

Assessment of risk of bias in included studies

Two review authors (YH and LY) independently assessed the methodological quality of eligible trials. We resolved disagreements by discussion, and if we could not reach a consensus, a third review author (QH) would arbitrate.

We performed risk of bias assessment using the 'Risk of bias' tool described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). A copy of the form we used to do this is provided in [Appendix 12](#).

We assessed each trial according to the following quality domains.

1. Random sequence generation and allocation concealment: These were considered as the criteria for assessing selection bias.
2. Blinding of participants and personnel: If it is assumed that participants are in VF, or in an intensive care unit, study outcomes may not be affected by blinding of participants. It would be unrealistic to blind EMS rescuers on the scene, and we consider that low risk of bias will occur even though EMS rescuers were not blinded. We considered blinding adequate if the physicians who provided medical treatment in hospital or an intensive care unit were blinded, regardless of blinding of participants and EMS personnel.
3. Blinding of outcome assessment: This was considered as the criterion for assessing detection bias and was assessed by determining whether outcome assessors were blind to the intervention.
4. Incomplete outcome data or loss to follow-up: These were assessed on the basis of the percentage of participants lost to follow-up and their distribution among the two groups.
5. Selective reporting.
6. Other potential sources of bias.

We planned to consider a trial as having low risk of bias if all domains were assessed as adequate. We planned to consider a trial as having high risk of bias if one or more domains were assessed as inadequate or unclear. We also planned to conduct sensitivity analyses to determine whether excluding studies at high risk of bias affects the results of the meta-analysis.

We completed the 'Risk of bias' table as part of the [Characteristics of included studies](#) and presented a 'Risk of bias summary' figure, which details all judgements made regarding all studies included in the review.

Measures of treatment effect

We measured risk ratios (RRs) and 95% confidence intervals (CIs) in dichotomous outcomes, including survival to hospital discharge, ROSC and long-term survival. We used RRs with 95% CIs to measure neurological outcomes, which had been grouped into the categories of 'good recovery' and 'unfavourable recovery' so they could be adapted for the meta-analysis.

Unit of analysis issues

We planned to reanalyse the data for the included cluster-randomized trial because they were incorrectly analysed in the original study. (The unit of allocation had been the individual participant.) However, we did not have sufficient information to reanalyse the RR for the included cluster-randomized trial. Therefore we used the available unadjusted data and went on to perform a sensitivity analysis so we could estimate how this would influence our meta-analysis.

Dealing with missing data

We contacted the first authors of included trials to obtain missing data necessary for a meta-analysis. We planned to conduct an intention-to-treat analysis of relevant trials if necessary.

Assessment of heterogeneity

We assessed clinical heterogeneity across studies by thoroughly inspecting the detailed clinical characteristics of the included trials, and we assessed the risk of bias as methodological heterogeneity.

We used the Chi² test of heterogeneity and considered P value ≤ 0.10 as presenting significant heterogeneity. We also used the I² statistic to assess heterogeneity. We planned to consider the heterogeneity important when I² was greater than 50% ([Higgins 2011](#)).

Assessment of reporting biases

We planned to use a funnel plot to assess publication bias if more than 10 studies were included in the review. We planned to test for funnel plot asymmetry according to the statistical methods described in [Rucker 2008](#).

Data synthesis

For data synthesis, all included outcomes were expressed as the RR and its 95% CI. We planned to use the random-effects model when the I² value was $> 50\%$; otherwise we planned to use the fixed-effect model.

We performed all analyses using [RevMan 5.1](#) software.

Subgroup analysis and investigation of heterogeneity

Our subgroup analysis of interest included the following variables.

1. Time interval from call receipt to arrival of EMS ($\leq$ four to five minutes or longer).
2. Cardiac arrest witnessed by bystanders (yes or no) (i.e. the participant's collapse was seen or heard by bystanders).
3. Causes of cardiac arrest (cardiac or non-cardiac aetiology).

Sensitivity analysis

We performed sensitivity analysis by including and excluding trials with moderate or high risk of bias. We also compared the two models of data synthesis: random-effects model and fixed-effect model.

Summary of findings

We used the principles of the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system ([Guyatt 2008](#)) to assess the quality of the body of evidence associated with specific outcomes (survival to hospital discharge, neurological outcomes

at hospital discharge, successful rate of ROSC, long-term survival) in our review and constructed a 'Summary of findings' (SoF) table using the GRADE software. The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. GRADE considers several factors potentially contributing towards total bias, including the following: risk of bias associated with study design (methodological quality), directness

of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

RESULTS

Description of studies

See [Figure 1](#); [Characteristics of included studies](#); and [Characteristics of excluded studies](#).

Figure 1. Study flow diagram.

Results of the search

Our electronic search of the four databases resulted in 3022 hits. After screening the titles and abstracts, we excluded duplicates. We excluded studies because they were of a non-randomized design or were not eligible according to our PICO criteria (population, intervention, comparison, outcome). We identified 16 studies for further inspection of the full texts. After reading the full texts, we excluded a further 12 studies and included a total of three RCTs and one cluster-randomized trial in our review.

Included studies

Three included trials used a randomized or quasi-randomized parallel design ([Baker 2008](#); [Jacobs 2005](#); [Wik 2003](#)), and one trial used a cluster-randomized design ([Stiell 2011](#)). We included four trials with a total of 3090 participants. Two of the trials were undertaken in Australia and enrolled patients in urban areas ([Baker 2008](#); [Jacobs 2005](#)). The third trial was conducted in Norway in an urban area ([Wik 2003](#)). The fourth trial ([Stiell 2011](#)), which used a cluster-randomized design, was conducted in 10 US and Canadian regional EMS systems constituting the Resuscitation Outcomes Consortium (ROC). Twenty subunits of the 10 ROC centres were designated as "clusters" according to their EMS agencies or geographic boundaries. Three trials included participants with non-traumatic OHCA witnessed by bystanders, and the rhythms were confirmed to be VF or pulseless VT by EMS paramedics when they arrived ([Baker 2008](#); [Jacobs 2005](#); [Wik 2003](#)). [Stiell](#) and colleagues included all arrest rhythms ([Stiell 2011](#)), we extracted the data of participants whose rhythms were confirmed to be VF or pulseless VT by EMS paramedics and still the sample size was the largest (2432 participants) when compared with the other three trials. No significant differences were noted between the two study groups in terms of baseline characteristics such as age, gender, ratio of witnessed SCA, provision of bystander CPR or response rate from collapse to ambulance arrival.

All four included trials carried out comparisons between a control group and a CPR first group. Participants in the standard group received immediate defibrillation as soon as the rhythms were confirmed as shockable, whilst those in the CPR group first received

CPR for one and one-half to three minutes and then defibrillation. In [Stiell 2011](#), the control group received 60 seconds of CPR before defibrillation versus 180 seconds for the delayed defibrillation group ([Stiell 2011](#)). In all included studies, participants would have received some CPR until rhythm analysis and defibrillation equipment were applied. This was likely to occur according to a similar time frame as that seen in the [Stiell](#) study control group, so we felt it was acceptable to include the [Stiell 2011](#) study. Other treatment strategies such as chest compressions, tracheal intubation, drug administration and shock regimens were provided according to the life support guidelines recommended by the European Resuscitation Council (ERC) ([Wik 2003](#)), the Australian Resuscitation Council (ARC) ([Baker 2008](#); [Jacobs 2005](#)) and the ROC training protocol for EMS providers, respectively.

Three trials reported survival to hospital discharge and ROSC ([Baker 2008](#); [Jacobs 2005](#); [Wik 2003](#)). Two trials reported the one-year survival rate ([Jacobs 2005](#); [Wik 2003](#)). Three trials reported neurological outcomes at hospital discharge ([Baker 2008](#); [Wik 2003](#); [Stiell 2011](#)). Three included trials reported subgroup data in the comparison of primary outcome according to whether response time (time interval from collapse to EMS arrival) was greater than five minutes ([Baker 2008](#); [Jacobs 2005](#); [Wik 2003](#)), but only one individual trial reported subgroup data on one-year survival ([Wik 2003](#)). Neither treatment produced adverse effects.

Excluded studies

We identified several observational studies; their characteristics are listed in the [Characteristics of excluded studies](#) table. One study ([Jost 2010](#)) used a randomized controlled design and studied the effects of CPR first versus immediate defibrillation. This study was excluded simply because the duration of initial CPR before defibrillation was only 60 seconds ([Jost 2010](#)).

Risk of bias in included studies

Assessment of risk of bias is shown in the [Characteristics of included studies](#) table and in [Figure 2](#) and [Figure 3](#). We considered three trials ([Baker 2008](#); [Stiell 2011](#); [Wik 2003](#)) to have low risk of bias and one trial ([Jacobs 2005](#)) to have high risk of bias.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Three studies are included.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Baker 2008	?	+	?	+	+	+	+
Jacobs 2005	-	-	?	+	+	+	+
Stiell 2011	?	+	+	+	+	+	+
Wik 2003	?	+	?	+	+	+	+

Allocation

Two trials reported the use of sealed opaque envelopes for concealment of allocation (Baker 2008; Wik 2003). Envelopes containing randomization cards and treatment assignment were opened immediately after the electrocardiogram had been verified by paramedics, but unfortunately the details of random sequence generation were not reported in either of these trials (Baker 2008; Wik 2003). So although we considered allocation concealment to be adequate, we considered the random sequence generation to be unclear. One trial used a quasi-randomized design because randomization was performed according to the ambulance case number (Jacobs 2005). We considered this study to have high risk of selection bias.

In the case of Stiell 2011 (Stiell 2011), no detailed information about random sequence generation was found in the article. The

ROC investigators designed the study using cluster-randomization, so recruitment bias and baseline imbalance were considered according to the "Assessing risk of bias in cluster-randomized trials" portion of Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Clusters were randomized at once, so lack of allocation concealment was considered. However, all clusters were assigned to cross over to the other strategy one or more times during the study at fixed intervals, and no important significant differences in baseline characteristics were found between the two groups. Also the between-group difference in primary outcome was adjusted for baseline characteristics. So no significant baseline imbalance was noted. Additionally, regarding the explicit diagnostic criteria of cardiac arrest, we considered this study to have low risk of recruitment bias.

Blinding

EMS personnel could not be blinded in these trials. Hospital personnel in three trials were blinded (Baker 2008; Jacobs 2005; Wik 2003), including the physicians responsible for follow-up treatments in hospital and the physicians responsible for outcomes assessments. In the case of Stiell 2011, although no blinding was performed during CPR phase or follow-up treatments, all rescuers implemented high-quality electronic monitoring of the CPR process, and adherence to protocol-specified performance targets was monitored throughout the study by a study monitoring committee, which provided regular feedback to site staff members. As participants initially were in VF and then were transferred to the intensive care unit after ROSC, blinding of participants might not have affected outcomes. Thus, we considered the four trials as having relatively low risk of performance and detection bias.

Incomplete outcome data

The four trials had complete follow-up (Baker 2008; Jacobs 2005; Stiell 2011; Wik 2003). So we considered that risk of attrition bias in all four trials was low.

Selective reporting

Although no original protocols of the trials have been obtained, the core outcomes of participants with OHCA as recommended by the Utstein style had been reported in all trials (Cummins 1991). So we consider the four trials as having low risk of reporting bias.

Other potential sources of bias

In the case of Stiell 2011, which used a cluster-randomized design, incorrect analysis was also assessed. The analysis was conducted at the level of individuals in this trial, but differences between the two treatment groups were statistically adjusted to the clustering, according to the article, although no detailed information was reported. So we considered it an unclear risk of incorrect analysis. We found the results of this trial to be consistent with those of other individual RCTs.

No other potential sources of bias (such as conflicts of interest) were found in the four included trials.

Effects of interventions

See: [Summary of findings for the main comparison CPR plus delayed defibrillation versus immediate defibrillation: overall analysis](#)

Primary outcomes

Survival to hospital discharge

(See Analysis 1.1.)

Three trials reported survival to hospital discharge as a primary outcome (Baker 2008; Jacobs 2005; Wik 2003), and neurological outcomes at hospital discharge were reported as the primary outcome in one trial (Stiell 2011). No individual trial showed a significant difference in the overall comparison of survival versus hospital discharge. Statistical heterogeneity among the three trials was significant according to the χ^2 test and the I^2 statistic ($\chi^2 = 10.78$, degrees of freedom (df) = 5, P value 0.06, $I^2 = 54\%$), and we used a random-effects model for meta-analysis. The pooled result (including 338 controls and 320 cases) also showed no difference

in survival to hospital discharge between the control group and the CPR first group (RR 1.09, 95% CI 0.54 to 2.20).

Secondary outcomes

Neurological outcomes at hospital discharge

(See Analysis 1.2.)

Three trials assessed neurological outcomes at hospital discharge by cerebral performance category (CPC); a good recovery was defined as a CPC score of 1 or 2. No significant difference was shown in any of the individual studies (Baker 2008; Jacobs 2005; Wik 2003). One trial assessed neurological outcomes at discharge using the modified Rankin scale; a satisfactory functional status was defined as a score of three or less (Stiell 2011). No significant difference was shown in this individual study. Although this is a cluster-randomized study, we failed to perform correct analysis for meta-analysis because needed data were not found. A random-effects model was used according to the assessment of heterogeneity. The pooled result showed no difference in good neurological recovery at hospital discharge between the study groups overall (RR 1.12, 95% CI 0.65 to 1.93, $\chi^2 = 8.83$, df = 4, P value 0.07, $I^2 = 55\%$).

Rate of return of spontaneous circulation (ROSC)

(See Analysis 1.3.)

All trials reported ROSC rates (Baker 2008; Jacobs 2005; Wik 2003). No difference was found in the individual trials (Baker 2008; Jacobs 2005; Wik 2003). A random-effects model was used for meta-analysis, and no significant difference was found (RR 0.94, 95% CI 0.77 to 1.15, $\chi^2 = 4.55$, df = 4, P value 0.34, $I^2 = 12\%$).

Survival at one year

(See Analysis 1.4.)

Two trials evaluated survival rate at one year (Jacobs 2005; Wik 2003). Overall results showed no significant difference between treatment groups in either of the two individual trials. According to meta-analysis, a random-effects model was used and no difference was observed in the pooled result (RR 0.77, 95% CI 0.24 to 2.49, $\chi^2 = 6.93$, df = 2, P value 0.03, $I^2 = 71\%$).

Subgroup analysis

All trials included participants with non-traumatic VF/VT; however no trials reported subgroup data according to whether bystander CPR was given. We therefore performed subgroup analysis according to the time interval between call receipt by EMS and the arrival of paramedics. One trial did not report subgroup results according to the EMS arrival interval (Stiell 2011), and another trial did not report subgroup results of neurological outcomes at discharge, ROSC rates and survival at one year (Jacobs 2005); so we contacted study authors by e-mail, but no further data were forthcoming. Therefore, we analysed data from these two trials in a single subgroup. Three trials performed subgroup analysis of survival to hospital discharge (Baker 2008; Jacobs 2005; Wik 2003), two trials performed subgroup analysis of neurological outcomes at hospital discharge and ROSC rates (Baker 2008; Wik 2003) and only one trial compared one-year survival according to the response time of the paramedics (Wik 2003).

When the response interval was five minutes or less (see [Analysis 1.1](#); [Analysis 1.2](#); [Analysis 1.3](#); and [Analysis 1.4](#)), pooled results showed that over a period of one and one-half to three minutes, CPR did not improve survival to hospital discharge compared with defibrillation immediately (RR 1.60, 95% CI 0.89 to 2.87, $\text{Chi}^2 = 1.17$, $\text{df} = 2$, P value 0.56, $I^2 = 0\%$). In the comparison of neurological outcomes at hospital discharge (RR 1.75, 95% CI 0.88 to 3.48, Chi^2 value 0.29, $\text{df} = 1$, P value 0.59, $I^2 = 0\%$) and ROSC rates (RR 1.01, 95% CI 0.75 to 1.36, $\text{Chi}^2 = 0.15$, $\text{df} = 1$, P value 0.69, $I^2 = 0\%$), pooled results showed no differences between study groups.

One trial ([Wik 2003](#)) compared survival at one year in two study groups and found no significant differences.

When the interval was longer than five minutes (see [Analysis 1.1](#); [Analysis 1.2](#); [Analysis 1.3](#); and [Analysis 1.4](#)) in the comparisons of survival to hospital discharge (RR 0.63, 95% CI 0.17 to 2.34, $\text{Chi}^2 = 7.04$, $\text{df} = 2$, P value 0.03, $I^2 = 72\%$), of neurological recovery at hospital discharge (RR 0.57, 95% CI 0.06 to 5.03, $\text{Chi}^2 = 5.99$, $\text{df} = 1$, P value 0.01, $I^2 = 83\%$) and of ROSC rates (RR 0.87, 95% CI 0.52 to 1.44, $\text{Chi}^2 = 4.03$, $\text{df} = 1$, P value 0.04, $I^2 = 75\%$), no differences were found between the two treatment groups in pooled results after meta-analysis. The random-effects model was used according to the heterogeneity assessment.

One trial ([Wik 2003](#)) ($n = 64$ and $n = 55$ for intervention and control groups, respectively) showed that CPR provided over three minutes before delayed defibrillation improved survival to hospital discharge (RR 7.17, 95% CI 1.74 to 29.57), CPC assessment at hospital discharge (RR 5.59, 95% CI 1.32 to 23.68) survival at one year (RR 6.66, 95% CI 1.60 to 27.66) and ROSC rates (RR 1.81, 95% CI 1.32 to 2.47) compared with immediate defibrillation when response time was greater than five minutes.

Sensitivity analysis

Results of sensitivity analysis including survival to hospital discharge, ROSC rate and one-year survival were not changed when we excluded studies with high risk of bias (according to allocation concealment and blinding; see [Analysis 2.1](#); [Analysis 2.2](#); [Analysis 2.3](#)). In the comparison of neurological outcomes, all three included studies were assessed as having low risk of bias ([Baker 2008](#); [Stiell 2011](#); [Wik 2003](#)).

Different model choices (fixed-effect model or random-effects model) did not change the effects of our results: survival to hospital discharge (fixed-effect RR 1.02, 95% CI 0.67 to 1.54; random-effects RR 1.09, 95% CI 0.54 to 2.20); neurological outcomes at hospital discharge (fixed-effect RR 1.05, 95% CI 0.90 to 1.22; random-effects RR 1.12, 95% CI 0.65 to 1.93); ROSC (fixed-effect 0.93, 95% CI 0.77 to 1.13; random-effects RR 0.94, 95% CI 0.77 to 1.15) and one-year survival (fixed-effect RR 0.81, 95% CI 0.47 to 1.39; random-effects RR 0.77, 95% CI 0.24 to 2.49).

We also performed sensitivity analysis for the cluster-randomized trial ([Stiell 2011](#)). Exclusion of this trial did not change the results in the comparison of good neurological recovery at hospital discharge (including this trial RR 1.08, 95% CI 0.63 to 1.83; excluding this trial RR 1.04, 95% CI 0.40 to 2.67).

Publication bias

As only four studies were included, we have not carried out funnel plots to evaluate publication bias in the current version of this review. We will include funnel plots in updates of this review, as further studies are conducted and published.

DISCUSSION

Summary of main results

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Overall completeness and applicability of evidence

All four included trials were conducted in adult participants with non-traumatic OHCA with VF or pulseless VT dysrhythmias present when the EMS paramedics arrived. All four trials comprised cases in urban areas. These trials were conducted in different countries (Norway, Australia, United States and Canada), and advanced life support methods were provided according to relevant national guidelines. It was believed that the degree of clinical heterogeneity secondary to differences between these guidelines was negligible because no evidence has been found to demonstrate any significant differences between the effects of different resuscitation guidelines or protocols. Therefore, we combined the results of all four trials for meta-analysis, including participants of different genders, ages and races. In most cases, the cause of OHCA was primarily a cardiac event. It should be noted that prehospital care was provided by different EMS systems in the different studies.

Quality of the evidence

We considered the risk of selection bias in two trials ([Baker 2008](#); [Wik 2003](#)) to be unclear. In the cluster-randomized trial of [Stiell 2011](#), random sequence generation was unclear, but risk of recruitment bias was low and baseline imbalance was noted ([Stiell 2011](#)). Risk of performance and detection bias in one trial was low ([Stiell 2011](#)), and risk of performance and detection bias in the other three trials ([Baker 2008](#); [Jacobs 2005](#); [Wik 2003](#)) was unclear. We found low risk of attrition bias and reporting bias across all included studies. We were unclear on the effect of the incorrect original analysis in the cluster-randomized trial ([Stiell 2011](#)). We are of the opinion that this would not lead to biased estimates of effect but may have created falsely small confidence intervals in the analysis of this study. No other potential sources of bias were discovered. Therefore, relatively good quality data were available for three studies ([Baker 2008](#); [Stiell 2011](#); [Wik 2003](#)), although we believed that the [Jacobs 2005](#) study possessed a relatively high risk of bias caused by inadequate allocation (potential for high risk of selection bias). In the overall analysis and subgroup analysis of participants with an EMS response time of five minutes or less, results of the three trials remained consistent. On subgroup analysis, we found inconsistent results when response time was greater than five minutes. One trial showed improved outcomes (survival to hospital discharge; neurological recovery at hospital discharge; rate of ROSC; survival at one year) for the CPR first group ([Wik 2003](#)). Although the effects observed in this trial were statistically significant, the study was underpowered as a result of insufficient sample size, and meaning valid conclusions still cannot be drawn.

We used the GRADE system to assess the quality of the body of evidence. Against these criteria, we considered the quality of evidence associated with survival to hospital discharge, neurological outcome at hospital discharge, ROSC and survival at one year as LOW. Details are provided in the 'Summary of findings' table ([Summary of findings for the main comparison](#)). Because a study with high risk of bias was included in the analysis of survival to hospital discharge, ROSC and survival at one year ([Jacobs 2005](#)), we considered the risk of bias in these categories to be serious enough to warrant downgrading of the quality of evidence for these three outcomes by one level. For neurological outcome at hospital discharge, the downgrading decision was derived from the serious inconsistency of results across the included studies. Also the imprecision was serious enough to downgrade the quality of evidence for all outcomes by one level.

Potential biases in the review process

As noted above, our decision to combine studies was based on the similarity of the resuscitation guidelines used. Other potential sources of heterogeneity should be considered in relation to our findings. The proportion of participants with a response time of five minutes or less in the trial conducted in Norway was different from the proportion in the other trials, which was conducted in Australia and North America; this difference may be related to the different EMS systems used ([Baker 2008](#); [Jacobs 2005](#); [Stiell 2011](#); [Wik 2003](#)) and may be related to the fact that the proportions of witnessed cardiac arrest and bystander CPR were not the same across trials. The time of initial CPR before defibrillation ranged from one and one-half to three minutes. Such variability would bring clinical heterogeneity. Additionally, important statistical heterogeneity was implied according to the Chi² test and the I² value, and we used a randomized-effects model in the overall analysis and the subgroup analyses. Therefore heterogeneity may have had an effect on our pooled results in meta-analysis.

A cluster-randomized trial was included in our meta-analysis. Because data were insufficient, we failed to perform correct analyses for this trial. Thus, it should be noted that this cluster-randomized trial might receive much greater weight in the meta-analysis. However, the results of this trial are consistent with those of the other included trials, and after sensitivity analysis was performed, the pooled results were not subject to change after this cluster-randomized trial was excluded.

An important limitation of our review is that only four clinical trials met the inclusion criteria. The search for trials in this review was extensive, and we searched both English and Chinese databases; however, only a small number of clinical trials were eligible for our analysis. This may influence the precision of our results, which should be interpreted with caution.

Agreements and disagreements with other studies or reviews

A randomized controlled trial conducted in Paris enrolled 845 participants and studied the effects of 60 seconds of CPR before defibrillation on the outcomes of participants with OHCA ([Jost 2010](#)). A randomized controlled trial conducted in Asia showed that CPR before rhythm analysis did not improve the rate of survival to hospital discharge ([Ma 2012](#)), but this study was not included in our review because it included participants with non-shockable rhythms.

Some observational studies on this topic were also performed. One prospective cohort study, which was conducted in Seattle and enrolled a total of 1117 participants, suggested that when the response interval was greater than four minutes, the provision of 90 seconds of initial CPR before defibrillation was associated with increased numbers of participants discharged alive and with favourable neurological function ([Cobb 1999](#)). One retrospective study identified 6674 participants ([Koike 2011](#)) but found equivocal one-month survival in the CPR first group when compared with the shock first group. A retrospective cohort study conducted in Japan enrolled 143 participants and showed that CPR before defibrillation improved neurological outcomes compared with immediate defibrillation ([Hayakawa 2009](#)). Although another prospective observational study showed no significant differences between the two study groups ([Bradley 2010](#)), we have not included these observational studies because of the absence of randomization or blinding, which may affect the quality of the results. The high risk of allocation bias in particular in observational studies might be important factor contributing to different results from those in the RCTs.

Above all, these findings are consistent with those of our analysis: It seems that current evidence is not sufficient to support the theory that initial CPR should be performed by EMS rescuers before defibrillation in patients with OHCA with VF/pulseless VT.

Two recent systematic reviews compared the effects of the two treatments on survival to hospital discharge ([Meier 2010](#); [Simpson 2010](#)). The criteria for eligible studies in these two reviews were similar to ours. In the case of [Simpson 2010](#), risk of bias of included trials was assessed according to the methodology recommended by The Cochrane Collaboration ([Higgins 2011](#)); only one outcome was studied (survival to hospital discharge), and the same three studies were included as ours. In the case of [Meier 2010](#), the quality of each trial was assessed using the Jadad scale ([Jadad 1996](#)), the same four outcomes were studied as ours and four studies were included ([Baker 2008](#); [Jacobs 2005](#); [Jost 2010](#); [Wik 2003](#)). The results of qualitative and quantitative analysis of these two reviews were similar to ours. However we believe we have added value to the literature, as we have performed a more up-to-date electronic search (May 2013) and have searched a Chinese database (China Academic Journal Network Publishing Database). We used the Cochrane 'Risk of bias' tool ([Higgins 2011](#)) to assess the risk of bias of included studies, and we have assessed the quality of the evidence according to GRADE principles ([Guyatt 2008](#)).

AUTHORS' CONCLUSIONS

Implications for practice

Owing to the low quality of the evidence summarised in this review, we have not been able to determine that CPR plus delayed defibrillation and immediate defibrillation are similarly effective. Two other systemic reviews have addressed the topic ([Meier 2010](#); [Simpson 2010](#)), and the results of these meta-analysis also demonstrate that outcomes are equivocal for CPR before defibrillation as compared with immediate defibrillation.

Although a more up-to-date search (May 2013) was performed in our review, and even though we also included a Chinese database (China Academic Journal Network Publishing Database), no further eligible RCTs were identified. After assessing the quality of the included studies according to a optimized methodology

(Guyatt 2008; Higgins 2011), we suggest that the quality of the present evidence in the literature is not sufficient to allow strong conclusions. In addition, the two previous reviews and our review show a signal toward possible superiority of predefibrillation CPR when the EMS response interval is longer than five minutes. However, we suggest that the quality of the evidence in this subgroup is particularly poor, and the statistical power is insufficient because of the low sample size, even when data are pooled.

The main conclusion that we can draw is that evidence is insufficient to enable us to draw strong conclusions on whether CPR before defibrillation is superior or even has an effect similar to that of immediate defibrillation. Further rigorous studies are required.

Implications for research

Many obstacles are encountered in setting up clinical studies investigating OHCA, mainly because of the variability and urgency of the emergency setting, the pressures on EMS and ethical concerns, so a cluster random design might be suggested. Currently, only a few studies have focused on the priority of CPR and defibrillation for adult participants with non-traumatic OHCA. Further rigorous studies enrolling larger numbers of participants

are needed. Adequate randomization and allocation concealment are very important, whilst care needs to be taken to accurately describe methodological information in future studies. Moreover, the heterogeneity of the variables in CPR must be considered, such as response times, bystander CPR, witnessed or non-witnessed cardiac arrest and clinical management by the EMS. Appropriate subgroup analysis may help. Also the most potentially beneficial time of CPR before defibrillation may still be defined by further studies.

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an observational study. *Lancet* 2007;**369**:920-6. [MEDLINE: 17368153]

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Baker 2008

Methods	Randomized controlled trial
Participants	<p>Adult participants with non-traumatic out-of-hospital cardiac arrest. Cardiac arrest was not witnessed by paramedics and presented with VF or pulseless VT when EMS paramedics arrived</p> <p>Total number of participants: 202; participating sites: South Australian Ambulance Service (SAAS)</p> <p>Intervention group: median age: 65.0 years; 83.5% male; cardiac arrest witnessed by bystanders: 83.5%; bystander performed CPR: 58.8%; settings: 82.5% in urban settings</p> <p>Control group: median age: 66.0 years; 80.0% male; cardiac arrest witnessed by bystanders: 79.0%; bystander performed CPR: 58.0%; settings: 83.8% in urban settings</p>
Interventions	<p>Intervention group: 3 minutes of CPR provided by paramedics before first defibrillation after the arrival of EMS personnel</p> <p>Control group: immediate defibrillation at the arrival of EMS personnel</p> <p>Defibrillation strategy and another advanced life support regimen such as epinephrine administration were provided according to the Australian Resuscitation Council (ARC) guidelines for CPR</p>
Outcomes	<p>Survival to hospital discharge</p> <p>Neurological outcomes at hospital discharge: cerebral performance category (CPC)</p> <p>Rate of return of spontaneous circulation (ROSC)</p>

Baker 2008 (Continued)

Notes

Recruitment was from 1 July 2005, to 31 July 2007

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization design; details of random sequence generation were not described in the text
Allocation concealment (selection bias)	Low risk	Central randomization; allocation was performed according to sequentially numbered opaque sealed envelopes on the scene
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Physicians responsible for follow-up treatments in hospital were blinded. EMS personnel were not blinded, but we considered that this had minimal effects on the rescue treatment. Because participants were in VF or in the intensive care unit, we considered that blinding of participants might not have affected outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physicians responsible for outcomes assessment were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up was reported
Selective reporting (reporting bias)	Low risk	Main outcomes of out-of-hospital cardiac arrest were reported in full
Other bias	Low risk	We did not identify other sources of bias

Jacobs 2005

Methods	Randomized controlled trial
Participants	<p>Adult patients with non-traumatic out-of-hospital cardiac arrest; cardiac arrest was not witnessed by paramedics and presented with VF or pulseless VT on arrival of the EMS paramedics</p> <p>Total number of participants: 256; participating sites: The study was undertaken in Perth by the South Australian Ambulance Service (SAAS)</p> <p>Intervention group: median age: 64.2 years; 79.8% male; cardiac arrest witnessed by bystanders: 73.9%; bystander performed CPR: 53.8%; settings: all urban settings</p> <p>Control group: median age: 61.9 years; 80.3% male; cardiac arrest witnessed by bystanders: 79.5%; bystander performed CPR: 63.5%; settings: all urban settings</p>
Interventions	<p>Intervention group: 90 seconds of CPR provided by paramedics before first defibrillation after arrival of EMS personnel</p> <p>Control group: immediate defibrillation at arrival of EMS personnel</p> <p>Defibrillation strategy and another advanced life support regimen such as epinephrine administration were provided according to the Australian Resuscitation Council (ARC) guidelines for CPR</p>
Outcomes	Survival to hospital discharge

Jacobs 2005 (Continued)

Survival at 1 year

Notes	Recruitment was from June 2000 to June 2002	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomization design; randomization was performed by way of the ambulance case number
Allocation concealment (selection bias)	High risk	No adequate allocation concealment was used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Physicians responsible for follow-up treatments in hospital were blinded. EMS personnel were not blinded, but we considered this to have minimal effects on the rescue treatment. As participants were in VF or in the intensive care unit, we considered that blinding of participants might not have affected outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physicians responsible for outcomes assessments were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up was reported
Selective reporting (reporting bias)	Low risk	Main outcomes of out-of-hospital cardiac arrest recommended by the Utstein style, including survival to hospital discharge, were reported
Other bias	Low risk	We did not identify other sources of bias

Stiell 2011

Methods	Cluster-randomized controlled trial	
Participants	<p>Adult participants with non-traumatic out-of-hospital cardiac arrest who were treated with defibrillation, delivery of chest compressions, or both, by EMS providers; cardiac arrest was not witnessed by paramedics</p> <p>Total number of participants: 9933; participating sites: The study was conducted in United States and Canada by the Resuscitation Outcomes Consortium (ROC)</p> <p>Intervention group: age: 66.7 ± 16.6 years; 63.9% male; cardiac arrest witnessed by bystanders: 43.7%; bystander performed CPR: 41.0%; settings: all urban settings</p> <p>Control group: age: 66.7 ± 16.6 years; 64.4% male; cardiac arrest witnessed by bystanders: 43.8%; bystander performed CPR: 39.7%; settings: all urban settings</p>	
Interventions	<p>Intervention group: received 3 minutes of chest compressions and ventilations (sufficient time to place defibrillator electrodes) before electrocardiographic analysis</p> <p>Control group: received 30 to 60 seconds of CPR and ventilations before ECG analysis</p> <p>Defibrillation strategy and another advanced life support regimen were provided according to ROC training protocol for EMS providers</p>	
Outcomes	Survival to hospital discharge	

Cardiopulmonary resuscitation (CPR) plus delayed defibrillation versus immediate defibrillation for out-of-hospital cardiac arrest (Review)

21

Stiell 2011 (Continued)

Neurological outcomes at hospital discharge: cerebral performance category (CPC)

ROSC

Notes Recruitment was from 2007 to 2009

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization design; details of random sequence generation were not described in the text
Allocation concealment (selection bias)	Low risk	Intervention was randomly allocated according to cluster assignment. Resuscitation Outcomes Consortium (ROC) investigators designed the study, and each of the 10 participating ROC centres (or sites) was divided into approximately 20 subunits, according to EMS agency or geographic boundaries, or according to defibrillator device, ambulance, station or battalion. Cluster-randomization was used in this study, so we considered that lack of concealment of an allocation sequence should not be an important issue. Baseline imbalance was considered. All clusters were assigned to cross over to the other strategy 1 or more times during the study at fixed intervals, and no important significant differences in baseline characteristics were noted between the 2 groups. So no significant baseline imbalance was considered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Single-blinded design was used. EMS personnel were not blinded, but in this study, all rescuers implemented high-quality electronic monitoring of the CPR process, and adherence to protocol-specified performance targets was monitored throughout the study by a study monitoring committee, which provided regular feedback to sites As participants were in VF or in the intensive care unit, we considered that blinding of participants might not have affected outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No blinding of outcome assessment was reported in this article. but we considered that this led to minimal effects on assessment of outcomes, including survival rate, ROSC rate and neurological performance score. Also, adherence to requirements for data submission was monitored throughout the study by a study monitoring committee
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up was reported
Selective reporting (reporting bias)	Low risk	Main outcomes of out-of-hospital cardiac arrest were reported in full
Other bias	Low risk	We did not identify other sources of bias

Wik 2003

Methods	Randomized controlled trial
Participants	Adult participants with non-traumatic out-of-hospital cardiac arrest; cardiac arrest was not witnessed by paramedics and presented with VF or pulseless VT on arrival of the EMS paramedics

Wik 2003 (Continued)

Total number of participants: 200; participating sites: The study was conducted in the Oslo EMS in Norway

Intervention group: median age: 71 years; 85% male; cardiac arrest witnessed by bystanders: 91%; bystander performed CPR: 62%; settings: all urban settings

Control group: median age: 70 years; 89% male; cardiac arrest witnessed by bystanders: 94%; bystander performed CPR: 56%; settings: all urban settings

Interventions	<p>Intervention group: 3 minutes of CPR provided by paramedics before first defibrillation after arrival of EMS personnel</p> <p>Control group: immediate defibrillation upon arrival of EMS personnel</p> <p>Defibrillation strategy and another advanced life support regimen such as epinephrine administration were provided according to the European Resuscitation Council (ERC) guidelines for CPR</p>
Outcomes	<p>Survival to hospital discharge</p> <p>Neurological outcomes at hospital discharge: cerebral performance category (CPC)</p> <p>Rate of return of spontaneous circulation (ROSC)</p> <p>Survival at 1 year</p>
Notes	Recruitment was from June 1998 to May 2001

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization design; details of random sequence generation were not described in the text
Allocation concealment (selection bias)	Low risk	Central randomization; allocation was performed according to sequentially numbered opaque sealed envelopes on the scene
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Physicians responsible for follow-up treatments in hospital were blinded. EMS personnel were not blinded, but we considered that this brought minimal effects on the rescue treatment. As participants were in VF or in the intensive care unit, we considered that blinding of participants might not have affected outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Physicians responsible for outcomes assessments were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up was reported
Selective reporting (reporting bias)	Low risk	Main outcomes of out-of-hospital cardiac arrest were reported in full
Other bias	Low risk	We did not identify other sources of bias

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aufderheide 2010	Not randomized design; focused on CPR strategy according to the 2005 AHA guidelines, including use of impedance threshold device
Bradley 2010	Prospective multi-centre observational study, time of CPR before defibrillation was ≤ 45 seconds in the control group and between 46 and 195 seconds in the intervention group
Cobb 1999	Prospective cohort study
Gottschalk 2002	CPR and defibrillation were provided not only by EMS but also by emergency medical technicians (EMTs); time of initial CPR varied from our criteria
Hayakawa 2009	Retrospective analysis of prospectively recorded data
Iwami 2007	Prospective observational study, focused on CPR provided by bystanders
Jost 2010	In intervention group, 60 seconds of CPR was provided by paramedics before the first defibrillation after the arrival of EMS personnel
Koike 2011	Retrospective analysis
Ma 2012	Participants with non-shockable rhythms were also included
Meier 2010	Meta-analysis
Simpson 2010	Meta-analysis
Stotz 2003	Retrospective study, and CPR duration was not eligible

DATA AND ANALYSES

Comparison 1. CPR plus delayed defibrillation versus immediate defibrillation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival to hospital discharge	3	658	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.54, 2.20]
1.1 CPR time interval ≤ 5 minutes	3	153	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.89, 2.87]
1.2 CPR time interval > 5 minutes	3	505	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.17, 2.34]
1.3 CPR time not reported	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Good neurological recovery at hospital discharge	3	2834	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.65, 1.93]
2.1 CPR time interval ≤ 5 minutes	2	111	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.88, 3.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 CPR time interval >5 minutes	2	291	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.06, 5.03]
2.3 CPR time not reported	1	2432	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.89, 1.24]
3 ROSC	3	658	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.77, 1.15]
3.1 CPR time interval ≤5 minutes	2	111	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.75, 1.36]
3.2 CPR time interval >5 minutes	2	291	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.52, 1.44]
3.3 CPR time not reported	1	256	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.39, 1.93]
4 Survival at 1 year	2	456	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.24, 2.49]
4.1 CPR time interval ≤5 minutes	1	81	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.67, 3.20]
4.2 CPR time interval >5 minutes	1	119	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.04, 0.76]
4.3 CPR time not reported	1	256	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.40, 3.73]

Analysis 1.1. Comparison 1 CPR plus delayed defibrillation versus immediate defibrillation, Outcome 1 Survival to hospital discharge.

Analysis 1.2. Comparison 1 CPR plus delayed defibrillation versus immediate defibrillation, Outcome 2 Good neurological recovery at hospital discharge.

Analysis 1.3. Comparison 1 CPR plus delayed defibrillation versus immediate defibrillation, Outcome 3 ROSC.

Analysis 1.4. Comparison 1 CPR plus delayed defibrillation versus immediate defibrillation, Outcome 4 Survival at 1 year.

Comparison 2. Sensitivity analysis: does the methodological quality influence the effects?

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival to hospital discharge (studies with low risk of bias)	2	402	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.41, 2.53]
2 ROSC (studies with low risk of bias)	2	402	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.73, 1.19]
3 Survival at 1 year (studies with low risk of bias)	1	200	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.39, 1.34]

Analysis 2.1. Comparison 2 Sensitivity analysis: does the methodological quality influence the effects?, Outcome 1 Survival to hospital discharge (studies with low risk of bias).

Analysis 2.2. Comparison 2 Sensitivity analysis: does the methodological quality influence the effects?, Outcome 2 ROSC (studies with low risk of bias). **Analysis 2.3. Comparison 2 Sensitivity analysis: does the methodological quality influence the effects?, Outcome 3 Survival at 1 year (studies with low risk of bias).** **APPENDICES****Appendix 1. CENTRAL search strategy**

#1 MeSH descriptor Electric Countershock explode all trees
#2 MeSH descriptor Ventricular Fibrillation explode all trees
#3 MeSH descriptor Tachycardia, Ventricular explode all trees
#4 defibrillation or ventricular (fibrillation or ventricular tachycardia or cardioversion* or (electric near shock*)):ti,ab
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Cardiopulmonary Resuscitation explode all trees
#7 MeSH descriptor Heart Massage explode all trees
#8 (life support or chest compression or CPR or (card* near resuscitat*)):ti,ab
#9 MeSH descriptor Heart Arrest explode all trees
#10 MeSH descriptor Death, Sudden explode all trees
#11 ((cardiac or heart or cardiopulmonary) near arrest):ti,ab or (sudden near death*):ti,ab
#12 (#6 OR #7 OR #8)
#13 (#9 OR #10 OR #11)
#14 (#5 AND #12 AND #13)

Appendix 2. Ovid MEDLINE search strategy

1 exp Electric Countershock/ or exp Ventricular Fibrillation/ or exp Tachycardia, Ventricular/ or (defibrillation or ventricular fibrillation or ventricular tachycardia or cardioversion* or (electric adj5 shock*)):mp.
2 exp Cardiopulmonary Resuscitation/ or exp Heart Massage/ or (life support or chest compression or cpr).mp. or (card* adj3 resuscitat*).mp.
3 1 and 2

4 exp Heart Arrest/ or exp Death, Sudden/ or ((cardiac or heart or cardiopulmonary) adj3 arrest).mp. or (sudden adj5 death*).mp.

5 3 and 4

6 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.

7 5 and 6

Appendix 3. Ovid EMBASE search strategy

1. cardioversion/ or heart ventricle fibrillation/ or heart ventricle tachycardia/ or (defibrillation or ventricular fibrillation or ventricular tachycardia or cardioversion* or (electric adj5 shock*)).ti,ab.

2. resuscitation/ or exp heart massage/ or (life support or chest compression or cpr).mp. or (card* adj3 resuscitat*).mp.

3. heart arrest/ or sudden death/ or ((cardiac or heart or cardiopulmonary) adj3 arrest).ti,ab. or (sudden adj5 death*).ti,ab.

4. 1 and 2 and 3

5. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))).ti,ab.) not (animals not (humans and animals)).sh.

6. 4 and 5

Appendix 4. ISI Web of Science search strategy

#1 TS= (defibrillation or ventricular fibrillation or ventricular tachycardia or cardioversion* or (electric SAME shock*))

#2 TS=(life support or chest compression or cpr) or TS=(card* SAME resuscitat*)

#3 TS=((cardiac or heart or cardiopulmonary) SAME arrest) or TS=(sudden SAME death*)

#4 #1 and #2 and #3

Appendix 5. CNKI search strategy

1 exp Electric Countershock/ or exp Ventricular Fibrillation/ or exp Tachycardia, Ventricular/ or (defibrillation or cardioversion*).mp.

2 exp Cardiopulmonary Resuscitation/ or exp Heart Massage/ or (life support or chest compression or resuscitation).mp.

3 1 and 2

4 exp Heart Arrest/ or exp Death, Sudden/ or ((cardiac or heart or cardiopulmonary) adj3 arrest).mp.

5 3 and 4

6 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or randomly.ab. or trial.ab.) not (animals not (humans and animals)).sh.

7 5 and 6

Appendix 6. Study Selection Form

First author	Journal/Conference proceedings etc	Year

Appendix 7. Study eligibility

RCT/Quasi	Relevant participants (adult patients of age > 18) (suffering OHCA)	Relevant interventions (CPR with delayed defibrillation compared with defibrillate immediately)	Relevant outcomes (survival to hospital discharge) (Neurological outcomes at hospital discharge, rate of ROSC, survival at 1 year)
Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear

(Continued)

Do not proceed if any of the above answers are 'No.' If study is to be included in 'Excluded studies' section of the review, record below the information to be inserted into 'Table of excluded studies.'

Appendix 8. Eligible trials form

Code each paper	Author(s)	Journal/Conference proceedings etc	Year

Appendix 9. Participants and trial characteristics

Participant characteristics	
	Further details
Age (mean, median, range, etc)	
Sex of participants (numbers/%, etc)	
Disease status/type, etc (if applicable)	
Other	
Trial characteristics	
	Further details
Single centre/Multi-centre	
Country/Countries	
How was participant eligibility defined?	
How many people were randomly assigned?	
Number of participants in each intervention group	
Number of participants who received intended treatment	
Number of participants who were analysed	
Drug treatment(s) used	
Dose/Frequency of administration	

(Continued)

Duration of treatment (state weeks/months etc; if cross-over trial, give length of time in each arm)

Median (range) length of follow-up reported in this paper (state weeks, months or years or if not stated)

Time points when measurements were taken during the study

Time points reported in the study

Time points you are using in RevMan

Trial design (e.g. RCT/quasi-randomized)

Other

Appendix 10. Data extraction form

Outcomes	Reported in paper (circle)	Subgroups	Information available in paper (circle)
Primary outcome: survival to hospital discharge	Yes/No	Time of call-to-arrival interval (<4-5 minutes or longer)	Yes/No
Secondary outcomes:	Yes/No	Cardiac arrest witnessed by bystanders	Yes/No
Neurological outcomes at hospital discharge	Yes/No	Cause of cardiac arrest (cardiac aetiology)	Yes/No
Rate of ROSC	Yes/No		
Survival at 1 year	Yes/No		

Appendix 11. Data extraction form 2

For dichotomous data			
Code of paper	Outcomes (rename)	Intervention group (n) n = number of participants, not number of events	Control group (n) n = number of participants, not number of events
	Primary outcome: survival to hospital discharge		
	Secondary outcomes:		
	neurological outcomes at hospital discharge		

(Continued)

rate of ROSC

survival at 1 year

Appendix 12. Methodological quality

Random sequence generation

State here method used to generate allocation and reasons for grading

Grade (circle)

adequate (random)

inadequate (e.g. alternate)

unclear

Concealment of allocation

Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding

State here method used to conceal allocation and reasons for grading

Grade (circle)

adequate

inadequate

unclear

Blinding

Person responsible for care of participants in hospital

Yes/No

Outcome assessor

Yes/No

Other

Yes/No

Intention-to-treat

An intention-to-treat analysis is one in which all participants in a trial are analysed according to the intervention to which they were allocated, whether or not they received it

All participants entering trial

15% or less excluded

More than 15% excluded

Not analysed as 'intention-to-treat'

Unclear

WHAT'S NEW

Date	Event	Description
20 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

HISTORY

Protocol first published: Issue 4, 2012

Review first published: Issue 9, 2014

Date	Event	Description
12 September 2014	Amended	Acknowledgement section corrected

CONTRIBUTIONS OF AUTHORS

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Conceiving of the review: YH

Co-ordinating the review: YH

Undertaking manual searches: YH

Screening search results: YH, LY

Organizing retrieval of papers: YH

Screening retrieved papers against inclusion criteria: YH, LY, QH

Appraising quality of papers: YH, LY

Abstracting data from papers: YH, LY

Writing to authors of papers for additional information: YH, LY

Providing additional data about papers: YH, LY

Obtaining and screening data on unpublished studies: YH, LY

Managing data for the review: YH, LY

Entering data into Review Manager ([RevMan 5.1](#)): YH

Obtaining RevMan statistical data: YH, GL

Performing other statistical analysis not using RevMan: YH, GL

Interpreting data: QH, YH, AJ

Making statistical inferences: GL, YH, QH

Writing the review: YH, QH, AJ

Securing funding for the review:

Performing previous work that was the foundation of the present study: YH

Serving as guarantor for the review (one author): YH

Taking responsibility for reading and checking the review before submission: YH, QH, AJ

DECLARATIONS OF INTEREST

Yu Huang: none known.

Qing He: none known.

Li J Yang: none known.

Guan J Liu: none known.

Alexander Jones: none known.

SOURCES OF SUPPORT

Internal sources

- None, China.

External sources

- None, China.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Cardiopulmonary Resuscitation [*methods] [mortality]; Combined Modality Therapy [methods] [mortality]; Electric Countershock [*methods] [mortality]; Out-of-Hospital Cardiac Arrest [mortality] [*therapy]; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Adult; Humans