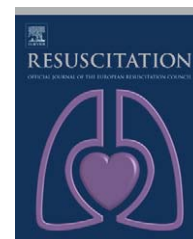




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CLINICAL PAPER

Cardiopulmonary resuscitation alone vs. cardiopulmonary resuscitation plus automated external defibrillator use by non-healthcare professionals: A meta-analysis on 1583 cases of out-of-hospital cardiac arrest[☆]

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KEYWORDS

Cardiopulmonary resuscitation (CPR);
Automated external defibrillator (AED);
Out-of-hospital CPR;
Meta-analysis

Summary

Background: Out-of-hospital cardiac arrest (OHCA) accounts for 250,000–350,000 sudden cardiac deaths per year in the United States. The availability of automated external defibrillators (AEDs) promoted the implementation of public access defibrillation programs based on out-of-hospital early defibrillation by non-healthcare professionals.

Aim of the study: To perform a systematic review and a meta-analysis of the pooled effect of studies comparing the outcome of pts receiving cardiopulmonary resuscitation plus AED therapy (CPR + AED) vs. cardiopulmonary resuscitation (CPR) alone, both delivered by non-healthcare professionals, for the treatment of OHCA.

Methods: We performed a search of the relevant literature exploring major scientific databases, carrying out a hand search of key journals, analysing conference proceedings and abstracts and discussing the topic with other researchers. Two analyses were planned to assess the outcomes of interest (survival to hospital admission and survival to hospital discharge).

Results: Three studies were selected for the meta-analysis. The first meta-analysis evidenced a RR of 1.22 (95% C.I.: 1.04–1.43) of surviving to hospital admission for people treated with

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CPR + AED as compared to CPR-only. The second meta-analysis showed a RR of 1.39 (95% C.I.: 1.06–1.83) of surviving to hospital discharge for people treated with CPR + AED as compared to CPR-only.

Conclusions: The results of our meta-analysis demonstrate that programs based on CPR plus early defibrillation with AEDs by trained non-healthcare professionals offer a survival advantage over CPR-only in OHCA. The conclusions of our meta-analysis add to previous evidence in favour of developing public-health strategies based on AED use by trained layrescuers.

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Background

Out-of-hospital cardiac arrest (OHCA) accounts for 250,000–350,000 sudden cardiac deaths (SCD) per year in the United States, thus representing a major public-health issue.^{1–5} OHCA may be caused by asystole, electromechanical dissociation, pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF).⁶ While the prognosis of asystole and electromechanical dissociation remains poor despite advanced life support, pulseless ventricular tachycardia and ventricular fibrillation, which are the presenting rhythm of OHCA in 41–70% of cases,^{7,8} can be effectively terminated by defibrillation. Unfortunately the probability of survival decreases of 5–10% per minute of delay in administration of defibrillation, thus making early defibrillation one of the most critical links in the chain of survival.⁶ In the past, defibrillation had been used by healthcare professionals only (physicians, nurses, paramedics, emergency medicine technicians) with manual defibrillators, which require expertise in rhythm recognition and extensive resuscitation algorithms knowledge. With the availability of automated external defibrillators (AEDs), which do not require expertise in rhythm recognition or extensive resuscitation algorithm knowledge, the opportunity of using defibrillation has been extended to non-healthcare professionals.

The great epidemiological burden of OHCA and the availability of AEDs promoted the implementation of Public Access Defibrillation programs based on out-of-hospital early defibrillation by non-healthcare professionals, and qualitative reviews on this topic have been published.⁹

Aim of the study

The aim of the present study was to perform a systematic review and a meta-analysis of the pooled effect of studies comparing standard cardiopulmonary resuscitation (CPR) to CPR + AED use by non-healthcare professional first responders for treatment of OHCA.

Methods

Identification of relevant studies

Studies eligible for our meta-analysis were those randomised trials comparing survival in patients with OHCA treated by CPR + AED vs. CPR-only, both performed by non-healthcare professional first responders. We carried out a

search of the relevant scientific literature using the Pubmed, Embase, Cochrane collaboration, Central Register of Controlled Trial databases and the “C2005 Evidence Evaluation Worksheets” which assisted the development of the ILCOR 2005 resuscitation guidelines. We also performed a hand search of major journals, discussed the topic with other researchers, explored conference proceedings and abstracts with the purpose of finding out other published studies. Limited attempt was made to identify unpublished studies. No limits were set on the searches in terms of date of publication or language. The end date of the search was 20/07/07.

The Pubmed search was performed using the keywords (automated external defibrillat*) OR (public access defibrillat*) and then restricted to 184 records with the search string proposed by Biondi-Zoccai et al.¹⁰ and reported in Appendix A.

The search in the Embase database was performed using the keywords “public access defibrillation” OR “automated external defibrillation” and retrieved 305 references.

The search in the Cochrane Library was performed using the following specifications: “public access defibrillation” in title, abstract and keywords OR “automated external defibrillator” in title, abstract, keywords and retrieved 27 articles.

The “Worksheet BLS—What is the safety, effectiveness and feasibility of AED programs?” was selected and analysed from the “C2005 Evidence Evaluation Worksheets” collection, arranged to assist the development of the ILCOR 2005 resuscitation guidelines.¹¹ From this worksheet we selected those studies with a level of evidence 1 or 2 that were defined as “randomised clinical trials or meta-analyses of multiple clinical trials with substantial treatment effects” and “randomised clinical trials with smaller or less significant treatment effects”, respectively.

Titles, abstracts and keywords of the selected articles were analysed independently by two researchers. Potentially eligible studies were retrieved and further analysed. The flow-chart of the study selection process is detailed in Figure 1. A targeted inquiry of major ongoing-trials databases was also performed to identify ongoing studies that may render the meta-analysis redundant. The inquiry of the United States National Institutes of Health ongoing-trial database at <http://www.clinicaltrials.gov> was performed selecting the keyword “automated external defibrillator” and retrieved six trials. The inquiry of the international ongoing-trial database at <http://www.controlled-trials.com> was performed selecting the keyword “automated exter-

nal defibrillator” and retrieved eight trials. None of the selected trials appeared to have the potential to render our analysis futile.

Quality assessment and data extraction

We assessed the quality of studies applying the JADAD scale scores.¹² The JADAD scale is aimed at ensuring quality of meta-analyses. The quality is assessed by five different items (description of randomisation, description of blinding, description of withdrawals and drop-outs, appropriate randomisation, appropriate blinding in allocation). The JADAD scores may range from -2 to 5. The scores for the selected studies were independently computed by two different researchers. A priori, a score of 3 or above was considered enough to qualify the study for the analysis.

Data extraction from studies was separately performed by two researchers. Data on survival to hospital admission and discharge between both the CPR plus automated external defibrillator treated group and the CPR-only treated group were analysed on the basis of the “intention to treat”.

Statistical analysis

Meta-analysis was performed using risks ratios (RRs) as a pooled effect estimate of treatment vs. control, since in the selected studies the considered outcomes were dichotomous. Random effects models were used to combine the data and statistical heterogeneity was assessed using the χ^2 test. Data were elaborated with the software Review Manager 4.2 (RevMan) for Windows.

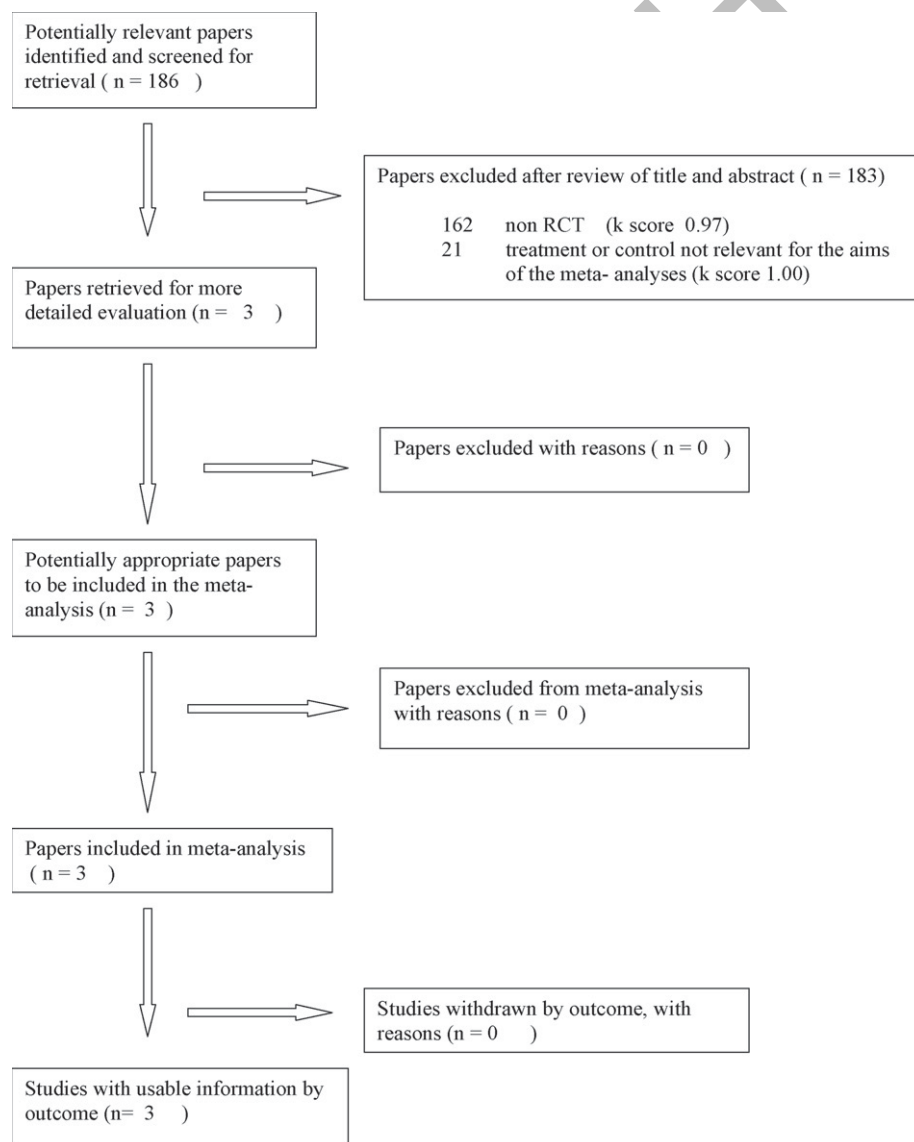


Figure 1 QUORUM statement flow-chart of study selection process.

Table 1 Characteristics and data of selected studies

	Kellerman et al. JAMA 1993	van Alem et al. BMJ 2003	Hallstrom et al. NEJM 2004
Active treatment	CPR + AED use by trained fire-fighters	CPR + AED use by trained fire-fighters or police	CPR + AED use by trained volunteer lay rescuers
Control treatment	CPR by trained fire-fighters	CPR by trained fire-fighters	CPR by trained volunteer lay rescuers
Treatment allocation	AED equipped areas vs. non AED equipped areas with cross-over	Cluster randomisation of AED equipped areas vs. non AED equipped areas with cross-over	Cluster randomisation of AED equipped areas vs. non AED equipped areas
Primary Endpoints	Survival at hospital admission Survival to hospital discharge Return of spontaneous circulation Neurological impairment	Survival at hospital admission Survival to hospital discharge Return of spontaneous circulation	Survival to hospital discharge
CPR + AED group (n)	447	243	107
Mean age (S.D.) in CPR + AED group	64.1 (15.3)	67 (14)	N.A.
Percentage (n) of men in CPR + AED group	60.9% (272)	77% (187)	N.A.
CPR-only group (n)	432	226	128
Mean age (S.D.) in CPR-only group	65.1 (15.2)	65 (14)	N.A.
Percentage (n) of men in CPR-only group	63.4% (274)	76% (172)	N.A.
Survival to admission	AED: 112 CPR: 101	AED: 103 CPR: 74	AED: 29 CPR: 50
Survival to discharge	AED: 40 CPR: 27	AED: 44 CPR: 33	AED: 30 CPR: 15
JADAD score	3	3	4

Results

Study selection process

The study selection process identified three studies eligible for the meta-analysis and their characteristics are summarised in Table 1.^{13–15} The selected studies were all clinical trials. The intervention in the trials was the use of AED by non-healthcare professional rescuers in addition to CPR before the arrival of emergency medical services (EMS). The controls for each of the trials were considered appropriate for the purposes of the analysis. In the trial by Kellermann et al. fire-fighters in the control group performed CPR until EMS arrival. In the trial by van Alem et al. police units,

but not fire-fighters, performed CPR until EMS arrival in the control group. In the study by Hallstrom et al. patients in the control group were attended by lay volunteers who performed CPR-only. *Randomisation.* The studies by van Halem and Hallstrom used cluster randomisation based on geographical areas, with a periodic cross-over design in the first one. The trial by Kellermann was defined by the authors as a non-randomised trial. However, allocation to active treatment or control was actually determined by chance depending on the availability of an AED on the fire-fighters rescue vehicle in the area; moreover a periodic cross-over design minimised bias. Additionally, the ILCOR 2005 scientific committee ranked this study as a *level of evidence 2* study (defined as “randomised clinical trials with smaller or less significant treatment effects”). *Setting.* All the studies

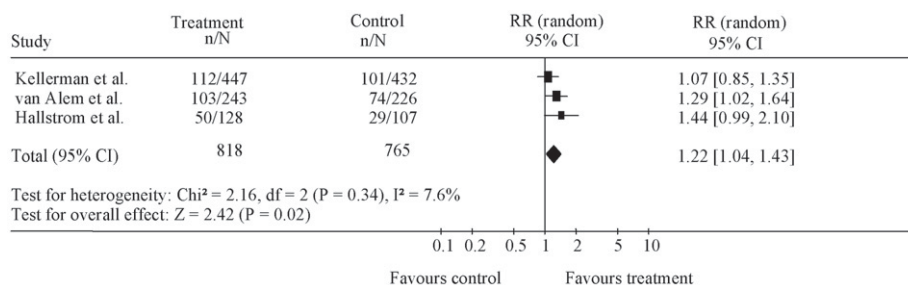


Figure 2 Meta-analysis: survival at hospital admission.

were carried out in the urban setting. *Blinding*. Blinding of patients and responders was not possible in any study.

Quality assessment and data extraction

Each of the selected studies was ranked of good quality according to the JADAD scale. The assigned scores were 3 for the study of Kellerman et al., 4 for the study of Hallstrom et al. and 3 for that of van Alem et al. Data on treatment allocation and survival to hospital admission and discharge were collected on 1583 cumulative cases of OHCA, and detailed results are presented in Table 1.

Statistical analysis

We performed two different meta-analyses on 1583 cases of OHCA exploring the effect of a CPR + AED vs. a CPR-only strategy deployed by lay rescuers on survival to hospital admission and on survival to hospital discharge.

The first meta-analysis evidenced a RR of 1.22 (95% C.I.: 1.04–1.43; $p=0.014$) of surviving at hospital admission for people treated with CPR + AED compared to CPR-only, and the chi square test did not show heterogeneity between studies ($p=0.34$) (Figure 2).

The second meta-analysis showed a RR of 1.39 (95% C.I.: 1.06–1.83; $p=0.019$) of surviving to hospital discharge for people treated with CPR + AED compared to CPR-only, and the chi square test did not show heterogeneity between studies ($p=0.70$) (Figure 3).

Considering a possible clustering in the studies, we performed a further analysis following the procedure described by Greenland,¹⁶ and found an OR pooled of 1.30 (95% CI: 1.06–1.61; p for homogeneity = 0.217) for the first meta-analysis, and of 1.51 (1.20–2.05; p for homogeneity = 0.784) for the second one, respectively.

Funnel plots relative to the first and the second meta-analyses are shown in Figure 4.

The number *needed to treat* (NNT) was also computed for the two endpoints. The number of out-of-hospital cardiac arrests to be treated by trained non-healthcare professionals by CPR + AED to gain one survival to hospital admission was 17 (NNT = 17). The number of out-of-hospital cardiac arrests to be treated by trained non-healthcare professionals by CPR + AED use to gain one survival to hospital discharge was 24 (NNT = 24).

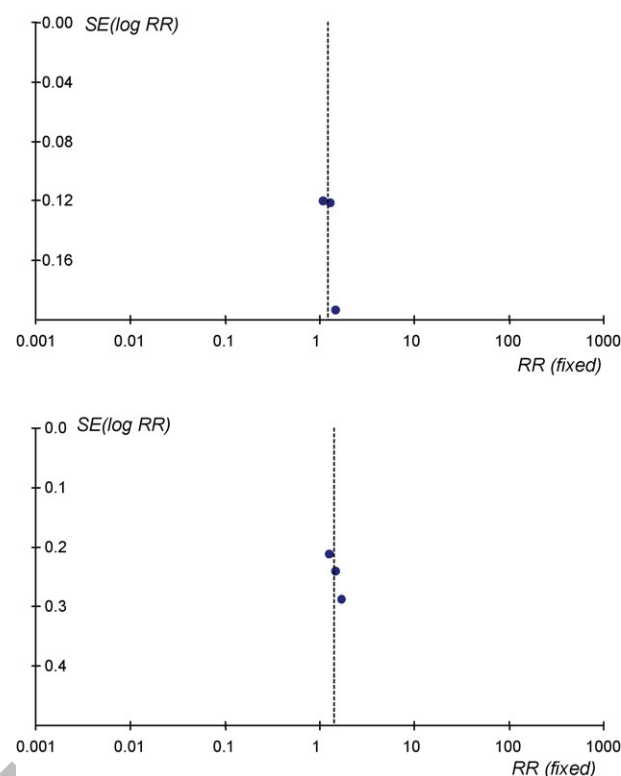


Figure 4 Funnel plot in relation to meta-analysis “survival to hospital admission” (top) and “survival to hospital discharge” (bottom).

Discussion

The great epidemiologic burden of sudden and unexpected cardiac death together with the availability of AEDs promoted the development of programs based on early defibrillation by non-healthcare professionals. However, clinical trials comparing CPR plus AED use by non-healthcare professionals against CPR-only before the arrival of EMS are only a few and show a modest benefit. In fact, even though the studies included in the analysis showed a survival benefit of being treating with an AED compared with CPR, none of them showed statistical significant confidence intervals, except for survival to hospital admission in the study by van Alem.

Usually, one of the aims of pooled analysis is to increase the power of the single studies, and in our case we obtained

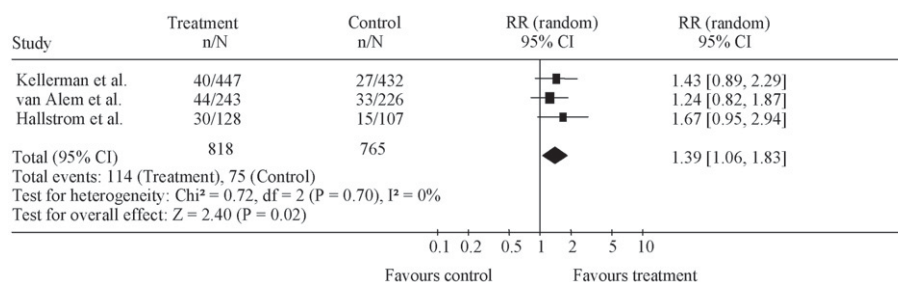


Figure 3 Meta-analysis: survival to hospital discharge.

results of individual trials adding up to 1583 cases of OHCA, demonstrating a survival benefit with significant 95% confidence intervals for both survival to hospital admission and discharge.

The results of a CPR + AED strategy delivered by lay rescuers are probably attributable to the recognised prognostic role of early defibrillation on those cardiac arrests with a shockable presentation rhythm.

We are aware of the limitations of our study. Resuscitation algorithms have changed significantly since the conduction of the studies included in our analysis. In more detail CPR-only before first shock delivery is currently advised for unwitnessed arrest, the chest compression–ventilation ratio and the DC shock delivery sequence has been modified. All of these modifications could significantly affect the results of similar analyses in the future. Moreover, the superiority of cardiac-only resuscitation over standard CPR has been recently emphasised.¹⁷ Additionally, several differences should be pointed out. First, the performance of police or fire-fighters based programs could be different from that of lay volunteers based programs. Second, in the study by van Alem et al. both fire-fighters and police units attended cardiac arrests and performed early defibrillation in the AED group, while in the control group cardiac arrest was attended only by fire-fighters (and not by police units) and this may have biased the results. Third, the AED was deployed by mobile rescue units in the studies by Kellermann and van Alem while it is not entirely clear how the AED was deployed in the study by Hallstrom. Finally, the trial by Kellermann was defined by the authors as a non-randomised trial, but as already pointed out the allocation to active treatment or control was actually determined by chance by the availability of an AED on the fire-fighter rescue vehicle so that even the ILCOR 2005 scientific committee ranked this study as a level of evidence 2 study (defined as “randomised clinical trials with smaller or less significant treatment effects”) in the development of international resuscitation guidelines. However, even in a sensitivity analysis excluding the study of Kellerman et al., the relative risks of survival to hospital admission and to hospital discharge still favoured the AED based approach (1.34 [1.09–1.64] and 1.38 [0.99–1.92], respectively).

The χ^2 test did not point out heterogeneity between studies, but we have to acknowledge that since the analysed trials are few the test had a low power; however, the p -values are higher than 0.10 which is the cut off often chosen when test power is low and the I^2 values are under 50%, thus allowing us to trust that studies are homogeneous enough. Finally, as funnel plots show (Figure 4), it is plausible that small studies with results worse than our pooled estimate were not published. The limited attempt to identify unpublished studies might have affected the results of our investigation.

Conclusion

The results of our meta-analysis demonstrate that programs based on CPR plus early defibrillation with AEDs by trained non-healthcare professionals offer a survival advantage over CPR-only in out-of-hospital cardiac arrest. The conclusions

of our meta-analysis add to previous evidence in favour of developing public-health strategies based on AED use by trained lay-rescuers.

Conflict of interest

The authors declare no conflict of interest.

Appendix A

Randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (clinical trial [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw]))) OR (latin square [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt])

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