Use of Cardiocerebral Resuscitation or AHA/ERC 2005 Guidelines Is Associated With Improved Survival from Out-of-Hospital Cardiac Arrest: A Systematic Review & Meta-Analysis

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<th>BMJ Open</th>
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<td>bmjopen-2012-001273</td>
</tr>
<tr>
<td>Article Type:</td>
<td>Research</td>
</tr>
<tr>
<td>Date Submitted by the Author:</td>
<td>25-Apr-2012</td>
</tr>
<tr>
<td>Complete List of Authors:</td>
<td>Salmen, Marcus; University of Colorado School of Medicine, Ewy, Gordon; University of Arizona Sarver Heart Center, Sasson, Comilla; University of Colorado, Department of Emergency Medicine</td>
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<td>Secondary Subject Heading:</td>
<td>Cardiovascular medicine, Emergency medicine</td>
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<tr>
<td>Keywords:</td>
<td>Adult cardiology &lt; CARDIOLOGY, Cardiology &lt; INTERNAL MEDICINE, ACCIDENT &amp; EMERGENCY MEDICINE</td>
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Use of Cardiocerebral Resuscitation or AHA/ERC 2005 Guidelines Is Associated With Improved Survival from Out-of-Hospital Cardiac Arrest: A Systematic Review & Meta-Analysis

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Keywords:
- Resuscitation
- Cardiac Arrest
- Emergency Medical Services
- Cardiocerebral

Word Count: 3,879
Abstract

Objective: To determine if use of Cardiocerebral Resuscitation (CCR) or AHA/ERC 2005 resuscitation guidelines improved patient outcomes from Out-of-Hospital Cardiac Arrest (OHCA) compared to older guidelines.

Design: Systematic review and meta-analysis

Data Sources: MEDLINE, EMBASE, Web of Science, and the Cochrane Library databases. We also hand-searched study references and consulted experts.

Study Selection: Design: randomized controlled trials and observational studies
Population: OHCA patients, age >17 years.
Outcome: Survival to hospital discharge
Quality: High or medium quality studies, as measured by the Newcastle Ottawa Scale (NOS) using pre-defined categories.

Results: Twelve observational studies met inclusion criteria. All 3 studies using CCR demonstrated significantly improved survival compared to use of AHA 2000 guidelines, as did 5 out of the 9 studies using AHA/ERC 2005 Guidelines. Pooled data demonstrates that use of a CCR protocol has an unadjusted Odds Ratio of 2.26 (95% Confidence Interval [CI]: 1.64-3.12) for survival to hospital discharge among all cardiac arrest patients. Among witnessed VF/VT patients, CCR increased survival by an OR of 2.98 (95% CI: 1.92–4.62). Studies using AHA/ERC 2005 Guidelines showed an overall trend towards increased survival, but significant heterogeneity existed among these studies.

Conclusions: We demonstrate an association with improved survival from OHCA when Cardiocerebral Resuscitation protocols or AHA/ERC 2005 Guidelines are compared to use of older guidelines. In the subgroup of patients with witnessed VF/VT, there was a three-fold increase in OHCA survival when CCR was used. CCR appears to be a promising resuscitation protocol for EMS providers in increasing survival from OHCA. Future research will need to be conducted to directly compare AHA/ERC 2010 guidelines with the CCR approach.
Introduction
Out-of-hospital cardiac arrest (OHCA) is a major cause of global mortality and a significant public health concern. In the US alone, an estimated 300,000 people suffer an OHCA each year, and only 7% will survive to hospital discharge.\(^1\) The survival rate had previously remained unchanged for over three decades despite a dramatic increase in our understanding of OHCA and its predictors of survival.\(^2\)

International standards for the emergency treatment of OHCA have existed since 1966, and the American Heart Association (AHA) published its first set of formal guidelines for CPR in 1992.\(^3\)\(^-\)\(^4\) Updates to the AHA and European Resuscitation Council (ERC) Guidelines in 2000 and 2005 reflected, in large part, a growing understanding of the electrophysiological phases of cardiac arrest and the need to minimize interruptions in chest compressions.\(^5\)\(^-\)\(^6\) Concurrently, animal and human studies have indicated that active ventilation during resuscitation may be unnecessary, and even detrimental.\(^7\)\(^-\)\(^8\) This has lead to the development of a new body of EMS (Emergency Medical Services) resuscitation protocols that minimize ventilation and maximize the amount of time spent by EMS doing chest compressions. One such protocol is Cardiocerebral Resuscitation (CCR), which emphasizes passive ventilation, continuous chest compressions, and delayed intubation. CCR was first instituted in 2003 as an alternative resuscitation protocol due to poor survival rates observed using the standard guidelines.\(^9\)\(^-\)\(^10\) At the time, CCR represented a significant departure from the AHA 2000 Guidelines because of its use of a single defibrillator shock instead of triple stacked shocks. This key resuscitation element was later incorporated into AHA and ERC 2005 Guidelines, and CCR has since shown promise in improving survival from OHCA.\(^11\)\(^-\)\(^12\)

While a majority of EMS systems continue to use AHA or ERC-based guidelines for CPR, a growing number have adopted the CCR protocol. To date, no systematic review has been conducted to compare standard AHA/ERC Guidelines to CCR protocols. Although the AHA Guidelines have several minor differences from the ERC Guidelines, we considered them similar enough in their strategies for ventilations, compressions, and defibrillations to be grouped together for the purposes of this review. This is the first systematic review and meta-analysis of the literature to examine the OHCA survival impact of EMS transitions from use of AHA/ERC 2000 Guidelines to use of a CCR protocol or AHA/ERC 2005 Guidelines.
Methods

This systematic review and meta-analysis was performed according to guidelines set forth by the MOOSE (Meta-Analysis Of Observational Studies in Epidemiology) checklist. Planning and study design were done by two authors (MS, CS), and included creation of an electronic database (Microsoft Excel) with defined primary endpoints and variables of interest that can be obtained from study authors on request.

Search strategy

A search was conducted of the following databases: MEDLINE (Ovid) (via PubMed), 1950 to Dec 2011; EMBASE (Ovid), 1966 to 2011; Web of Science, 1970 to 2011; the Cochrane Central Register of Controlled Trials; the Cochrane Database of Systematic Reviews; the Database of Abstracts of Reviews of Effects; the NHS Economic Evaluation Database; and the Health Technology Assessment Database. Our search strategy included searching for keywords such as “cardiocerebral”, “minimally interrupted”, and “continuous compressions” (using truncation and adjacency techniques) from within the subject headings of “Heart Arrest”, “Resuscitation”, and “Emergency Medical Services”. Results were limited to human studies with English abstracts published since 2000. The full details of all the search strategies can be obtained from study authors on request. Additionally, we reviewed the bibliographies of included studies and published review articles, as well as sought expert opinion (GE) to obtain additional studies. The search included all through December 1, 2011.

Inclusion criteria

Studies were considered eligible for inclusion if they met criteria for study design, control protocol, study protocol, outcome, and methodological quality (Box 1). Similar to other recent studies, methodological quality was assessed using the Newcastle Ottawa Scale (NOS) for cohort studies, wherein studies are given up to nine total points for fulfilling criteria in Selection, Comparability, & Exposure. We categorized studies as high quality if they received eight or nine points, medium quality if they received six or seven points, and low quality if they received five points or less. Only high and medium quality studies were included in this review.

We excluded reviews, editorials, opinions, studies on bystander resuscitation, studies comparing the absence/presence of advanced life support, studies focusing on mechanical
devices, and studies available only as meeting abstracts. In addition, we excluded studies with non-English language full-text, studies meeting incomplete criteria for the resuscitation protocols, and studies containing duplicative data of the included studies.

To be considered for inclusion, studies must have explicitly stated use of AHA 2000 Guidelines or ERC 2000 Guidelines as their EMS “control” protocol. These studies had to directly compare EMS use of AHA 2000/ERC 2000 guidelines to either AHA 2005, ERC 2005, or CCR protocols. Cardiocerebral Resuscitation has several distinct and important differences from the AHA and ERC Guidelines for cardiopulmonary resuscitation, which are illustrated in Table 1. We defined an EMS study protocol to be a Cardiocerebral Resuscitation protocol if it contained four out of five critical elements12: 1) 200 chest compressions upon initial EMS arrival, 2) if indicated, administration of a single, direct shock, 3) immediate post-shock 200 chest compressions, 4) delayed intubation until after 3 full cycles, and 5) administration of epinephrine as soon as possible.

Study selection process

We screened citations in three stages (Figure 1). In Stage 1, one reviewer (MS) reviewed all citations by title or abstract to exclude clearly irrelevant and duplicate citations. In Stage 2, two reviewers (MS, CS) screened remaining abstracts for potential inclusion. In Stage 3, three reviewers (MS, CS, GE) reviewed the full text of all potentially eligible studies, and final inclusion was based on the agreement of all three investigators. Reviewers were not blinded to study authors or outcomes.

Data Extraction

Relevant information from the studies, including characteristics of the study population and outcome measures, was extracted by two reviewers (MS, CS) using the prepared extraction database (Microsoft Excel). Data on study characteristics (year, location), variables of interest (age, gender, witnessed arrest, bystander CPR, initial shockable rhythm, EMS response time), total patient numbers per group, and outcomes of relevant groups were extracted. When included, data was extracted directly from Utstein templates. Absolute numbers were recalculated when percentages were reported.
Data Analysis & Synthesis

Individual study data were used to calculate unadjusted odds ratios (OR) for survival to hospital discharge for each EMS “control” and EMS “study” (defined as either AHA 2005 or CCR) protocol. Outcome data of the included studies were combined within each group to estimate the pooled effect (odds ratio, OR) for the use of CCR compared to AHA 2000 and the use of AHA 2005 compared to AHA 2000. Because witnessed ventricular fibrillation is a commonly used measure of OHCA survival, we conducted a subgroup analysis of these patients to compare the control versus study protocols for AHA 2005 and CCR guidelines. Calculations were based on a DerSimonian and Laird random effects model. Heterogeneity among trials was quantified with Higgins’s and Thompson’s I2, which can be interpreted as the percentage of variability due to heterogeneity between studies rather than sampling error. Publication bias was assessed by generating separate Funnel Plots for each of the two groups of studies. Findings are presented as point estimates and 95% confidence intervals, and when appropriate, weight of individual studies. All analyses were performed within RevMan version 5.1.

Results

Identification and selection of studies

Our initial electronic search yielded 654 citations, and an additional 27 were identified through hand-search of bibliographies and other sources. After an initial screen of titles, 100 abstracts were reviewed, and 22 of those were subsequently selected for full-text review. Six studies were excluded for lacking sufficient number of CCR elements, three studies excluded for sharing duplicative data with included studies, and one study for non-English language text. Finally, 12 total studies satisfied the predetermined inclusion criteria: three using Cardiocerebral Resuscitation and nine using AHA 2005 or ERC 2005 Guidelines, as shown in Figure 1.

Characteristics of included studies

The final sample included 12 studies, with approximately 19,634 subjects. Study characteristics and pertinent outcome data are shown in Table 2. All 12 articles that were included were prospective observational studies with data on survival pre- and post-implementation of guidelines. Eight of the 12 studies were rated as high quality, and four were
rated as medium quality. No randomized controlled trials were identified that met inclusion criteria.

Three studies, which included a total of 2,820 subjects, met the predetermined criteria for use of AHA 2000 (control) versus CCR (study) protocol.\textsuperscript{18-20} Nine studies, which included a total of 16,814 subjects, compared the use of AHA 2000/ERC 2000 (control) versus AHA 2005/ERC 2005 (study) protocols.\textsuperscript{21-29}

Eight of the studies were conducted in North America, and one each in Taiwan, Norway, New Zealand, and Denmark. Data on EMS control protocols (2000 Guidelines) were collected in the range of 2003 to 2006, except for Kellum (2008) which began collecting data in 2001. Data on EMS study protocols (CCR or AHA/ERC 2005 Guidelines) were collected in the range of 2004 to 2008. Of note, none of the studies using CCR, but five of studies using AHA 2005 Guidelines explicitly reported consistent use of therapeutic hypothermia during the study period.\textsuperscript{21 23 25 26 28}

The mean subject age across all studies was 64 years, and the mean gender distribution was 66.4% male. Two studies had significant differences in age between their control and study populations.\textsuperscript{22 25}

There was a wide range across studies in the proportion of OHCA receiving bystander CPR (8% to 58%) with a mean of 34.6%. The mean EMS response time was 6.2 minutes, with a range of 4.7 to 9.3 minutes. The mean proportion of OHCA patients with a presenting rhythm of ventricular fibrillation or ventricular tachycardia was 29.9%, with a range of 5.6% to 50%. Three studies reported statistically significant differences in the proportion of witnessed arrest, proportion of bystander-CPR, or response time between control and study populations.\textsuperscript{20 22 23}

**Overall Outcomes**

Survival to hospital discharge was identified as the primary or secondary outcome in all studies. Mean survival when using AHA/ERC 2000 Guidelines was 6.9% (range of 1.8% to 11.1%). Mean survival to discharge increased to 10.1% (6.5% - 19.4%) when using AHA/ERC 2005 Guidelines, and to 9.3% (5.4% to 18.3%) when Cardiocerebral Resuscitation was used. Overall mean survival across all studies and protocols was 9.7%.

**AHA 2000 Guidelines as compared to CCR**

All three of the studies using a CCR protocol showed significantly improved survival for CCR compared to use of AHA 2000 Guidelines. Pooled analysis of data from these studies (Figure
demonstrated a statistically significant survival benefit when using a CCR protocol, with a pooled odds ratio of 2.26 (95% CI: 1.64 – 3.12). Heterogeneity among the studies was not significant (I² = 0.0%, p=0.61).

Subgroup analysis of the patients with a presenting rhythm of witnessed ventricular fibrillation/ventricular tachycardia showed a significant association with survival for the CCR protocol as compared to the AHA 2000 Guidelines. Pooled odds ratio of survival to hospital discharge for this subgroup was 2.98 (95% CI: 1.92 – 4.62) (Figure 2). The funnel plot of these three studies was not suggestive of publication bias (Supplemental Figure 1).

**AHA/ERC 2000 Guidelines as compared to AHA/ERC 2005 Guidelines**

Eight of the nine studies using AHA/ERC 2005 Guidelines demonstrated improved survival to hospital discharge for use of AHA/ERC 2005 compared to AHA/ERC 2000 guidelines, a result that was statistically significant in five out of nine studies (Figure 3). Although the overall trend was towards a survival benefit for AHA/ERC 2005 Guidelines, heterogeneity tests revealed significant heterogeneity among these nine studies (I² = 72%, p=0.0004), so a pooled odds ratio for survival was not calculated.

Subgroup analysis of the patients with a presenting rhythm of witnessed ventricular fibrillation/ventricular tachycardia showed a trend toward improved survival for the AHA/ERC 2005 Guidelines as compared to the AHA/ERC 2000 Guidelines. However, there was significant heterogeneity between studies so a pooled odds ratio was not calculated. The funnel plot of these nine studies was not suggestive of publication bias (Supplemental Figure 2).

**Discussion**

**Main Findings**

In our systematic review of 12 studies and 19,634 subjects, we found a consistent and significant survival benefit from out-of-hospital cardiac arrest when EMS transitioned to use of updated resuscitation protocols. Our meta-analysis findings suggest that, compared to AHA 2000 Guidelines, use of CCR has a significant association with increased survival for all OHCA patients. In our subgroup analysis of patients with a presenting rhythm of VF/VT, use of a CCR protocol was associated with nearly a 3-fold increase in survival. This association was not as clear in the comparison of the AHA/ERC 2000 to AHA/ERC 2005 Guidelines, as there was a trend toward improved survival, but a pooled odds ratio could not be calculated secondary to
heterogeneity between studies. Although a pooled estimate of effect was not possible for this set of studies, the 2005 updates to resuscitation guidelines appear to have led to a demonstrable effect on OHCA survival.

It appears that OHCA survival for both the CCR and AHA/ERC 2005 Guidelines is associated with an overall increase in survival from OHCA. After years of unchanged survival rates, this is a promising new finding. Furthermore, the association with improved survival is seen most clearly in the studies using a CCR protocol. Based on animal models and human studies, it is likely that multiple elements of the AHA/ERC 2005 Guidelines and CCR protocols have contributed to this progress. Both the AHA/ERC 2005 Guidelines and CCR emphasize the need to maintain coronary and cerebral perfusion pressure by minimizing interruptions in chest compressions, although CCR eliminates any stoppage for ventilations. The benefits of this emphasis on optimal chest compression depth and continuous rate of chest compressions have been shown in multiple animal studies.\(^{31-32}\) In addition, both protocols emphasize 150-200 compressions immediately prior and immediately after defibrillation attempts, in recognition of the evidence that a perfused heart is much more likely to convert to a pulsatile rhythm after shock.\(^{33-37}\) These changes endorsed by the AHA and ERC 2005 Guidelines have likely contributed heavily to the demonstrated progress in OHCA survival.

However, the most significant difference between AHA/ERC 2005 Guidelines and CCR protocols is the decision to delay intubation in favor of passive ventilation. An existing body of studies has shown that intubations can 1) cause significant delays and/or interruptions in chest compressions\(^{38}\), and 2) lead to excessive positive pressure ventilation which can reduce venous return, reduce cerebral and coronary perfusion pressures, and consequently reduce likelihood of survival.\(^{7-8}\)

The benefit of passive insufflation was recently shown in a sub-analysis of the “minimally interrupted cardiac resuscitation” protocol used in Arizona and included in this meta-analysis through Bobrow et al. (2008).\(^{39}\) Due to reluctance of EMS teams to forgo active ventilation, this protocol allowed airway management through either passive insufflation or bag-valve-mask ventilation, at the discretion of the paramedics. For the subset of patients most likely to survive (witnessed VF/VT), neurologically intact survival was significantly higher among patients who received passive insufflation only as compared to bag-valve mask (38.2% compared to 25.8%).\(^{39}\) Another study, published in 2011, showed an association with increased survival when a non-standard resuscitation protocol was implemented in Sussex County, United Kingdom.\(^{40}\) Delayed
ventilation was a key feature in this protocol; patients with witnessed OHCA and initial VF/VT
were not given any active ventilations until after three cycles of 100 compressions plus shock.
Using this strategy, survival in these patients increased from a historical baseline of 13% to
approximately 30%.

The newest ERC and AHA Guidelines were recently released in late-2010.\textsuperscript{41-42} The ERC
Guidelines have removed the recommendation for a specified period of CPR prior to first
defibrillation, while the AHA Guidelines have a strong emphasis on C-A-B: compressions, airway
and then breathing. The shift to focusing on providing quality chest compression at a rate of at
least 100 per minute is a change from the AHA 2000 and 2005 guidelines in which the airway
and breathing were first addressed. Although this is similar to the approach to CCR, there are
still significant differences, the most significant being that CCR encourages compressions without
ventilations. Future research will need to be conducted to directly compare survival between
use of the updated AHA and ERC 2010 Guidelines and use of CCR.

Limitations:

This systematic review yielded a total of 12 studies reporting results on CCR and
AHA/ERC 2005 Guidelines as compared to AHA/ERC 2000 Guidelines. This relatively small
sample limits the generalizability of our results in several ways. Only three studies reported
results from the use of CCR protocols, which limited the meta-analysis to include only 2820 total
subjects. Additionally, some of the included studies reported few total patients surviving to
hospital discharge, and thus were not as heavily weighted in the meta-analysis. However, even
with a small number of studies and total subjects, this meta-analysis was sufficiently powered to
demonstrate a significant survival benefit. Finally, although our Funnel Plots did not suggest a
significant publication bias, it is possible that unpublished, negative studies were
underrepresented in our review. Future research from multiple research centers across the U.S.
and internationally could potentially strengthen the results demonstrated here.

All of the included studies report data from observational studies; no randomized-
controlled trials were found that met inclusion criteria, and thus this review was unable to locate
studies of the highest scientific quality. Indeed, randomization of OHCA patients to different EMS
protocols is impractical and ethically problematic. All of the observational studies included in
this review were found to be of high or medium methodological quality based on the NOS, but
due to inherent weaknesses in observational studies there exists the potential for confounding
and bias within these studies. These potential confounders may include a number of possible changes to the emergency health care systems that occurred between the “control” and “study” protocols, such as community education or improved quality of chest compressions by EMS. Additionally, it is possible that the survival improvement demonstrated here with newer protocols is confounded by temporal changes in the communities studied. Changes in community demographics or disease burden that occurred between and within the periods of data collection could have contributed to the observed changes in survival. However, given the overall similarity in demographics and characteristics of the “control” and “study” subjects (as reported in the individual studies) this potential confounding is not likely to have had a significant influence on the overall results.

The introduction of therapeutic hypothermia represents another important possible limitation to the interpretation of these results. The use of post-arrest hypothermia was not consistent between “control” and “study” protocols of individual studies. Four of the nine studies using AHA 2005 Guidelines reported significantly increased use of therapeutic hypothermia during the “study” protocol period (two other studies did not mention change in hypothermia use). Given the strong evidence for the benefit of therapeutic hypothermia\textsuperscript{43-44}, it is thus likely that the use of hypothermia contributed to the overall trend towards improved survival; our analysis is limited in its ability to calculate the magnitude of that contribution. However, therapeutic hypothermia was not used on any of the patients included in the three CCR studies. Thus, it is extremely unlikely that hypothermia alone could be an alternative explanation for the increase in survival demonstrated by use of the CCR protocols.

The heterogeneity of the nine studies using AHA 2005 or ERC 2005 guidelines precluded pooling of their data and a summary estimate of effect. These studies were also heterogeneous in the specifics of the resuscitation protocols used, many employing minor deviations from the AHA or ERC guidelines. For example, both the “control” and “study” protocols of Sayre et al. (2009) utilized 2 minutes of CPR prior to first defibrillation attempt, and Steinmetz et al. (2009) utilized a mechanical compression device. Additionally, there exist minor but important differences between the AHA and ERC resuscitation guidelines. While these variations might have influenced the results of the individual studies, the random-effects model used for our pooled data analysis accounted for some of this variability. Still these variations serve to highlight the difficulty of standardizing resuscitation protocols and comparing EMS systems.
Although delayed intubation is one of the pillars of Cardiocerebral Resuscitation, the three studies included in the “AHA 2000 as compared to CCR” group all utilized different protocols for airway management during the “study” protocol time period. The Kansas City Missouri (KCMO) protocol used in Garza et al. (2009) used a 50:2 compression to ventilation ratio. Kellum et al. (2010) delayed intubation for patients with shockable rhythms only. Most significantly, Bobrow et al. (2008) allowed bag-valve-mask ventilation at the paramedics’ discretion. The differences in the airway management strategies of these three studies makes it more difficult to assess which aspects of the CCR protocol contributed most to increased survival, and limits the generalizability of our results.

Conclusions:

The results of this systematic review and meta-analysis demonstrate an association with survival from OHCA when CCR protocols or AHA/ERC 2005 Guidelines are compared to AHA/ERC 2000 Guidelines. Although no randomized trials have yet been reported, multiple high quality observational studies have demonstrated an association with increased survival post-AHA/ERC 2005 guideline or CCR implementation. Additionally, in the pooled subgroup of witnessed VF/VT patients, there was a three-fold increase in OHCA survival after a CCR protocol was implemented. The focus of the updated AHA 2010 and ERC 2010 Guidelines shifts emphasis toward providing uninterrupted, quality chest compressions. However these changes still do not incorporate key elements of the CCR protocol that this study indicates are associated with improved OHCA survival, such as passive insufflation and minimal interruptions of chest compressions. Our study suggests that CCR appears to be a promising resuscitation protocol for EMS providers in increasing survival from OHCA. Future research will need to be conducted to directly compare AHA/ERC 2010 Guidelines with the CCR approach.

Authors’ contributions: MS, CS conceptualized and designed this systematic review and meta-analysis. MS, CS were substantially involved in data acquisition (literature search, study selection, and data abstraction). MS, CS performed the analyses and were substantially involved in data interpretation. MS, GE, CS provided data used for the analysis and relevantly contributed to the interpretation and intellectual content of the manuscript. MS, CS drafted the manuscript. All authors revised the manuscript critically for important intellectual content. All authors approved the final version.

Funding: This project received no specific funding
Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Ethical approval: not required

Data sharing: available from authors upon request

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Box: Inclusion criteria for eligible studies

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<td>Out-of-Hospital Cardiac Arrest patients, &gt;18 years of age.</td>
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<td>EMS Study Protocol:</td>
<td>AHA 2005 Guidelines or ERC 2005 Guidelines for Cardiopulmonary Resuscitation, or Cardiocerebral Resuscitation</td>
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<tr>
<td>Outcomes:</td>
<td>Rate of bystander CPR, EMS response time, Proportion of initial VF/VT, and Survival to hospital discharge</td>
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<td>Quality:</td>
<td>High or Medium quality, as categorized using the Newcastle Ottawa Scale (NOS) for cohort studies.</td>
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Table 1: AHA vs ERC vs CCR Characteristics

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<th>Defibrillation</th>
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<td>Tracheal Intubation 10-12 breaths/min</td>
<td>Pre: --- * Triple Shock * * Pulse Check * Post: 1 min CPR</td>
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<td><strong>ERC 2000 CPR</strong></td>
<td>15:2 ratio</td>
<td>Tracheal Intubation ~12 breaths/min</td>
<td>Pre: --- * Triple Shock * * Pulse Check * Post: 1 min CPR</td>
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<td><strong>AHA 2005 CPR</strong></td>
<td>30:2 ratio</td>
<td>Tracheal Intubation 8-10 breaths/min</td>
<td>Pre: Optional 5 cyc * Single Shock * Post: 5 cycles * Pulse Check *</td>
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<td><strong>ERC 2005 CPR</strong></td>
<td>30:2 ratio</td>
<td>Tracheal Intubation 8-10 breaths/min</td>
<td>Pre: 2 min CPR * Single Shock * Post: 2 min CPR * Pulse Check *</td>
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<td><strong>Cardiocerebral Resuscitation (2003)</strong></td>
<td>Continuous 100/min</td>
<td>Passive Only; Delayed Intubation</td>
<td>Pre: 200 compress * Single Shock * Post: 200 compress * Pulse Check *</td>
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Figure 1: Flow chart depicting the outline of study selection process

654 potentially relevant citations identified through database searching

27 additional citations identified through hand-search of bibliographies and other sources

681 citations screened by title & abstract for potential inclusion

Excluded, n=5819
n=5819: Reviews, opinions, clear irrelevance, duplicates

100 potential citations for secondary review

Excluded, n=78
n=37: Comment, reviews, Utstein reports
n=20: Bystander CPR(dispatcher CPR
n=10: Only partial elements of CCR
n=4: Focus on EMS ACLS
n=4: Meeting abstracts only
n=3: Mechanical CPR devices

22 studies comparing AHA 2000, Guidelines to AHA 2005 Guidelines or CCR protocol

Excluded, n=10
n=6: Incomplete criteria for CCR
n=3: Duplicative data of included studies
n=1: Non-English language

3 studies meeting complete CCR criteria

Included in Review

9 studies of AHA guideline changes

Stage 1: Review of title or abstract

Stage 2: Review of abstract

Stage 3: Full-text review
Table 2: Characteristics and outcomes of included studies

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<th>Study</th>
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<th>Control vs. Study Protocol</th>
<th>Bystander CPR (%)</th>
<th>Response Time (min)</th>
<th>Initial VF/VT (%)</th>
<th>Total Arrests (n)</th>
<th>Survival to Discharge (n, %)</th>
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<td>Bobrow (2008)</td>
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<td>AHA 2000</td>
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<td>31.7</td>
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<td>MICR</td>
<td>39</td>
<td>5.2</td>
<td>29.9</td>
<td>668</td>
<td>36 (5.4%)</td>
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<td>Garza (2009)</td>
<td>Missouri</td>
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<td>AHA 2000</td>
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<td>5.4</td>
<td>31.4</td>
<td>1097</td>
<td>64 (5.8%)</td>
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<td>KCMO Protocol</td>
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<td>5.3</td>
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<td>339</td>
<td>37 (10.9%)</td>
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<td>Kellum (2008)</td>
<td>Wisconsin</td>
<td>High</td>
<td>AHA 2000</td>
<td>45</td>
<td>7.4</td>
<td>42.5</td>
<td>268</td>
<td>21 (7.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CCR</td>
<td>45</td>
<td>8.6</td>
<td>47.4</td>
<td>230</td>
<td>42 (18.3%)</td>
</tr>
<tr>
<td><strong>AHA/ERC 2005 Guidelines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aufderheide (2010)</td>
<td>MN, TX, NE, FL, NC</td>
<td>High</td>
<td>AHA 2000</td>
<td>38</td>
<td>5.6</td>
<td>25.3</td>
<td>1641</td>
<td>166 (10.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AHA 2005</td>
<td>40</td>
<td>5.6</td>
<td>23.9</td>
<td>1605</td>
<td>211 (13.1%)</td>
</tr>
<tr>
<td>Bigham (2011)</td>
<td>Canada &amp; USA</td>
<td>Medium</td>
<td>AHA 2000</td>
<td>29</td>
<td>5.8</td>
<td>23.1</td>
<td>5054</td>
<td>294 (5.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AHA 2005</td>
<td>35</td>
<td>5.7</td>
<td>24.2</td>
<td>2725</td>
<td>177 (6.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AHA 2005</td>
<td>35</td>
<td>5.4</td>
<td>24.1</td>
<td>410</td>
<td>47 (11.5%)</td>
</tr>
<tr>
<td>Hung (2010)</td>
<td>Taiwan</td>
<td>High</td>
<td>AHA 2000</td>
<td>8</td>
<td>4.7</td>
<td>5.6</td>
<td>463</td>
<td>47 (10.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AHA 2005</td>
<td>10</td>
<td>4.7</td>
<td>7.2</td>
<td>430</td>
<td>30 (7.0%)</td>
</tr>
<tr>
<td>Lick (2011)</td>
<td>Minnesota</td>
<td>High</td>
<td>AHA 2000</td>
<td>20</td>
<td>7.5</td>
<td>27.3</td>
<td>106</td>
<td>9 (8.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AHA 2005</td>
<td>29</td>
<td>7.2</td>
<td>36.4</td>
<td>247</td>
<td>48 (19.4%)</td>
</tr>
<tr>
<td>Olavevegen (2009)</td>
<td>Norway</td>
<td>Medium</td>
<td>ERC 2000</td>
<td>52</td>
<td>8</td>
<td>35</td>
<td>435</td>
<td>46 (10.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ERC 2005</td>
<td>58</td>
<td>9</td>
<td>34</td>
<td>482</td>
<td>63 (13.1%)</td>
</tr>
<tr>
<td>Robinson (2010)</td>
<td>New Zealand</td>
<td>Medium</td>
<td>AHA 2000</td>
<td>50</td>
<td>9.1</td>
<td>45</td>
<td>162</td>
<td>18 (11.1%)</td>
</tr>
<tr>
<td>Sayre (2009)</td>
<td>Ohio</td>
<td>High</td>
<td>AHA 2000</td>
<td>28</td>
<td>5.1</td>
<td>21.7</td>
<td>660</td>
<td>40 (6.1%)</td>
</tr>
<tr>
<td>Steinmetz (2008)</td>
<td>Denmark</td>
<td>Medium</td>
<td>ERC 2000</td>
<td>24</td>
<td>5</td>
<td>34.1</td>
<td>193</td>
<td>21 (10.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ERC 2005</td>
<td>28</td>
<td>5</td>
<td>43.3</td>
<td>226</td>
<td>41 (18.1%)</td>
</tr>
</tbody>
</table>

a Minimally Interrupted Cardiac Resuscitation (MICR) allowed either passive insufflation or bag-valve-mask ventilation at paramedic discretion
b Kansas City, Missouri (KCMO) Protocol included a 50:2 compression to ventilation ratio
c Values represent the sub-population of witnessed VF/VT
d Values are reported from “Phase 3” of the step-wise introduction of AHA 2005 guidelines
e These protocols represent the “Pre” and “Post” states of a community intervention
f Both protocols used 2 minutes of CPR prior to the first defibrillation
g This protocol used an automated compression device (AutoPulse™)
h Quality categorized as High, Medium, or Low using the Newcastle Ottawa Scale, similar to other recent meta-analyses.
Figure 2: Forest Plot of Pooled Odds Ratios: CCR vs. AHA 2000 Studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CCR Protocol Events</th>
<th>AHA 2000 Guidelines Total</th>
<th>Total Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bobrow (2008)</td>
<td>36</td>
<td>668</td>
<td>4</td>
<td>218</td>
</tr>
<tr>
<td>Garza (2009)</td>
<td>37</td>
<td>339</td>
<td>64</td>
<td>1097</td>
</tr>
<tr>
<td>Kellum (2008)</td>
<td>42</td>
<td>230</td>
<td>21</td>
<td>268</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1237</td>
<td>1583</td>
<td>100.0%</td>
<td>2.26 [1.64, 3.12]</td>
</tr>
<tr>
<td>Total events</td>
<td>115</td>
<td>89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.99, df = 2 (P = 0.61); I² = 0%
Test for overall effect: Z = 4.99 (P < 0.000001)

Favours AHA 2000 Favours CCR

Figure 3: Forest Plot of Odds Ratios for Witnessed VF/VT Survival: CCR vs. AHA/ERC 2000 Studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CCR Protocol Events</th>
<th>AHA 2000 Guidelines Total</th>
<th>Total Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bobrow (2008)</td>
<td>23</td>
<td>131</td>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>Garza (2009)</td>
<td>42</td>
<td>89</td>
<td>18</td>
<td>92</td>
</tr>
<tr>
<td>Kellum (2008)</td>
<td>25</td>
<td>63</td>
<td>32</td>
<td>143</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>283</td>
<td>278</td>
<td>100.0%</td>
<td>2.98 [1.92, 4.62]</td>
</tr>
<tr>
<td>Total events</td>
<td>90</td>
<td>52</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.32, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 4.87 (P < 0.000001)

Favours AHA 2000 Favours CCR

Figure 4: Forest Plot of Odds Ratios: AHA/ERC 2005 vs. AHA/ERC 2000 Studies

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td>Aufderheide 2010</td>
<td>211</td>
</tr>
<tr>
<td>Bigham (2011)</td>
<td>177</td>
</tr>
<tr>
<td>Hinchey (2010)</td>
<td>47</td>
</tr>
<tr>
<td>Hung (2010)</td>
<td>30</td>
</tr>
<tr>
<td>Lick (2011)</td>
<td>48</td>
</tr>
<tr>
<td>Olaveveengen (2009)</td>
<td>63</td>
</tr>
<tr>
<td>Robinson (2010)</td>
<td>20</td>
</tr>
<tr>
<td>Sayre (2009)</td>
<td>96</td>
</tr>
<tr>
<td>Steinmetz (2008)</td>
<td>67</td>
</tr>
</tbody>
</table>

Odds Ratio M–H, Random, 95% CI

Favours AHA 2000 Favours AHA 2005
References:


Supplemental Figure 1: Funnel Plot of CCR vs. AHA 2000 Studies

Supplemental Figure 2: Funnel Plot of AHA/ERC 2005 vs. AHA/ERC 2000 Studies
“Use of Cardiocerebral Resuscitation or AHA 2005 Guidelines Improves Survival from Out-of-Hospital Cardiac Arrest: Systematic Review & Meta Analysis”

Marcus Salmen, B.S.¹, Gordon Ewy M.D.², Comilla Sasson, M.D., M.S.³

MOOSE Checklist

<table>
<thead>
<tr>
<th>Table. A Proposed Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting of background should include</td>
</tr>
<tr>
<td>✓ Problem definition</td>
</tr>
<tr>
<td>✓ Hypothesis statement</td>
</tr>
<tr>
<td>✓ Description of study outcome(s)</td>
</tr>
<tr>
<td>✓ Type of exposure or intervention used</td>
</tr>
<tr>
<td>✓ Type of study designs used</td>
</tr>
<tr>
<td>✓ Study population</td>
</tr>
<tr>
<td>Reporting of search strategy should include</td>
</tr>
<tr>
<td>✓ Qualifications of searchers (e.g., librarians and investigators)</td>
</tr>
<tr>
<td>✓ Search strategy, including time period included in the synthesis and keywords</td>
</tr>
<tr>
<td>✓ Effort to include all available studies, including contact with authors</td>
</tr>
<tr>
<td>✓ Databases and registries searched</td>
</tr>
<tr>
<td>✓ Search software used, name and version, including special features used (e.g., explosion)</td>
</tr>
<tr>
<td>✓ Use of hand searching (e.g., reference lists of obtained articles)</td>
</tr>
<tr>
<td>✓ List of citations located and those excluded, including justification</td>
</tr>
<tr>
<td>✓ Method of addressing articles published in languages other than English</td>
</tr>
<tr>
<td>✓ Method of handling abstracts and unpublished studies</td>
</tr>
<tr>
<td>✓ Description of any contact with authors</td>
</tr>
<tr>
<td>Reporting of methods should include</td>
</tr>
<tr>
<td>✓ Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested</td>
</tr>
<tr>
<td>✓ Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)</td>
</tr>
<tr>
<td>✓ Documentation of how data were classified and coded (e.g., multiple raters, blinding, and interrater reliability)</td>
</tr>
<tr>
<td>✓ Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)</td>
</tr>
<tr>
<td>✓ Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results</td>
</tr>
<tr>
<td>✓ Assessment of heterogeneity</td>
</tr>
<tr>
<td>✓ Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis)</td>
</tr>
<tr>
<td>✓ Provision of appropriate tables and graphics</td>
</tr>
<tr>
<td>Reporting of results should include</td>
</tr>
<tr>
<td>✓ Graphical summarizing individual study estimates and overall estimate</td>
</tr>
<tr>
<td>✓ Table giving descriptive information for each study included</td>
</tr>
<tr>
<td>✓ Results of sensitivity testing (e.g., subgroup analysis)</td>
</tr>
<tr>
<td>✓ Indication of statistical uncertainty of findings</td>
</tr>
<tr>
<td>Reporting of discussion should include</td>
</tr>
<tr>
<td>✓ Quantitative assessment of bias (e.g., publication bias)</td>
</tr>
<tr>
<td>✓ Justification for exclusion (e.g., exclusion of non–English-language citations)</td>
</tr>
<tr>
<td>✓ Assessment of quality of included studies</td>
</tr>
<tr>
<td>Reporting of conclusions should include</td>
</tr>
<tr>
<td>✓ Consideration of alternative explanations for observed results</td>
</tr>
<tr>
<td>✓ Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)</td>
</tr>
<tr>
<td>✓ Guidelines for future research</td>
</tr>
<tr>
<td>✓ Disclosure of funding source</td>
</tr>
</tbody>
</table>

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
April 23rd, 2012

Richard Sands
Managing Editor
British Medical Journal Open

Manuscript ID: BMJ.2012.003830
Title: Use of Cardiocerebral Resuscitation or AHA/ERC 2005 Guidelines Is Associated with Improved Survival from Out-of-Hospital Cardiac Arrest: A Systematic Review & Meta-Analysis

Dear Mr. Sands:

We appreciate the thoughtful comments provided by the editors and reviewers and have incorporated their suggestions into a revised version of the manuscript. We believe the comments have substantially improved the manuscript and hope that it is now suitable for publication in the British Medical Journal Open. Below you will find a point-by-point response to the reviewers’ comments.

Please do not hesitate to contact me directly at marcus.salmen@ucdenver.edu if I can provide any further information or if you have additional questions. I look forward to hearing from you.

Best Regards,

Marcus Salmen, BS
University of Colorado School of Medicine
Aurora, Colorado
Responses to Reviewers’ Comments

1. “In general, the methods are sufficiently described. But a detailed assessment of the risk of bias and quality of the included studies is missing. First, the sources of bias in a non-randomized studies dealing with interventions may be significant, therefore a detailed description of potential bias of the individual studies are needed. In principle, the traditional tools for bias evaluation of randomized trials may be preferable. However, more specific tools for assessing methodological quality and risk of bias in non-randomized trial have been developed. The following references may bring adequately tools for these assessments.”

We agree with the reviewer that this is an important addition to the manuscript. We have taken the reviewer’s suggestion of using one of the standardized tools for assessing bias of observational studies. We have redone the analysis using the Newcastle Ottawa Scale (NOS) to better measure the methodological quality of the possible studies. As a result, we have now only included high and medium quality studies in the review. Please see the added changes to Box 1, the paragraph on inclusion criteria on page 3, and the paragraph on characteristics of included studies on page 5.

2. Secondly, the study design of the included studies has to be presented. How were the studies created (case-series, cohort, case-control, historical control, before-after comparison)? How was the data collected (consecutively, prospectively or retrospectively)?

We appreciate this suggestion. We have modified the paragraph on characteristics of included studies on page 5 to read: “All 12 articles that were previously included were prospective observational studies with data on survival pre- and post-implementation of guidelines.”

3. In a systematic review, a protocol should include pre-specified details and criteria for the methods used. Even though the authors state that planning, study design and extraction of endpoints were predefined, a protocol should also include the above mentioned assessments of the bias and quality of the individual studies. It should be pre-specified how to handle low quality/high bias studies. Should they be excluded from the meta-analyses, or should a sub-group analysis of high quality/low bias studies be presented as the main findings of the review? In other words, at one level the review needs a more thorough bias evaluation of the specific studies, and at another level the review must further clarify how the authors avoid to introduce bias in their extraction and interpretation of data in the meta-analyses/review.

We have added the assessment of methodological quality using the Newcastle Ottawa Scale to the methods section on page 3. We have also amended this section to more clearly state the process for including studies in the meta-analysis. Because of space limitations, we have not included the table below in the manuscript, but would be able to include this as an Appendix table. The specific NOS scores on quality are included below (Table 1).
Due to space limitations, we are not able to comment in detail on the specific bias present in each of the 12 included studies. However, we have included a more detailed assessment of bias in our discussion and limitations sections on page 9.

Appendix Table 1: Newcastle Ottawa Scale (NOS) Quality Scores of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Comparability</th>
<th>Exposure</th>
<th>Total</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bobrow</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>9</td>
<td>High</td>
</tr>
<tr>
<td>Garza</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>High</td>
</tr>
<tr>
<td>Kellum</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>High</td>
</tr>
<tr>
<td>Aufderheide</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>High</td>
</tr>
<tr>
<td>Bigham</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>Medium</td>
</tr>
<tr>
<td>Hinchey</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>High</td>
</tr>
<tr>
<td>Hung</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>High</td>
</tr>
<tr>
<td>Lick</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>High</td>
</tr>
<tr>
<td>Olasveengen</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>Medium</td>
</tr>
<tr>
<td>Robinson</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>Medium</td>
</tr>
<tr>
<td>Sayre</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>8</td>
<td>High</td>
</tr>
<tr>
<td>Steinmetz</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>Medium</td>
</tr>
</tbody>
</table>

4. It is stated that the absolute numbers were recalculated when percentages were reported. It has to be clarified if the presented odds ratios from the individual studies are adjusted or unadjusted. Furthermore, the pooled estimates must not be calculated based upon a mix of adjusted and unadjusted estimates. The odds ratios presented in the manuscript are “unadjusted”. We have added this language to first paragraph of the data analysis and synthesis section on page 5.

5. Interpretation and conclusions. The review is only based upon observationally studies and a more extensive bias control is needed. Therefore, the authors must make a more distinct reservation concerning the clinical impact of their findings. We agree with the reviewer that more reserved language is needed in making conclusions from this research. We have revised the conclusion section to reflect this on page 11. The revised manuscript states: “The results of this systematic review and meta-analysis demonstrate an association with survival from OHCA when CCR protocols or AHA/ERC 2005 Guidelines are compared to AHA/ERC 2000 Guidelines. Although no randomized trials have yet been reported, multiple high quality observational studies have demonstrated an association with increased survival post-AHA/ERC 2005 guideline or CCR implementation. Additionally, in the pooled subgroup of VF/VT patients, there was a three-fold increase in OHCA survival after a CCR protocol was implemented. The focus of the new AHA 2010 Guidelines shifts emphasis toward providing uninterrupted, quality chest compressions both before and after defibrillation. However this change still does not incorporate key elements of the CCR protocol that this study indicates are associated with improved OHCA survival, such as passive insufflation and minimal interruptions of chest compressions. Our study suggests...
that CCR appears to be a promising resuscitation protocol for EMS providers in increasing survival from OHCA. Future research will need to be conducted to directly compare AHA/ERC 2010 Guidelines with the CCR approach.”

6. The abstract does reflect the paper, however the title must be changed, as there is not robust evidence to conclude as written. The title may include statements as “...may improve survival...” or “...associated with increased survival.....”.

We appreciate the reviewer’s suggestion on this change. We have thus changed the title of the manuscript to be: “Use of Cardiocerebral Resuscitation or AHA/ERC 2005 Guidelines Is Associated with Improved Survival from Out-of-Hospital Cardiac Arrest: A Systematic Review & Meta-Analysis”

Reviewer 2:

Major Points

1. The authors ask a simple, but relevant, question: does treatment according to CCR or 2005 ALS guidelines perform better than the 2000 ALS guidelines? However, there are some limitations to this question: The 2005 guidelines from the American Heart Association (AHA) and the European Resuscitation Council (ERC) are not completely interchangeable and often small, but perhaps important, differences exists (and likewise for the 2000 guidelines) (major).

We agree with this reviewer’s comment that the AHA and ERC guidelines have important differences. We have decided to highlight some of these differences by including both the ERC 2000 and ERC 2005 Guidelines in Table 1, allowing for a direct comparison to the AHA Guidelines. However, we felt that for the purposes of this review, these protocols were similar enough to be treated as a single group, while noting the heterogeneity that exists within this group. We have added a sentence to the last paragraph of the introduction section, on page 2, "Although the AHA Guidelines have several minor differences from the ERC Guidelines, we considered them similar enough in their strategies for ventilations, compressions, and defibrillations to be grouped together for the purposes of this review.” Additionally, we have decided to consistently use the term “AHA/ERC Guidelines” throughout the manuscript.

2. The fact that the authors are unable to locate studies of a high scientific quality is, of course, not their fault. However, this limits the usability of the review and meta-analysis significantly (major) and should be covered in the discussion in detail.

We appreciate this comment. As stated above, we have made changes to the study design and manuscript to more fully address the methodological quality of the included studies. Also, we have additional limitations on page 9 to further highlight the importance of this: “All of the included studies report data from observational studies; no randomized-controlled trials were found that met inclusion criteria, and thus this review was unable to locate studies of the highest
3. The exact objective raised by the authors in the last line of the introduction is not clear. Do they compare CCR and ALS 2005 to ALS 2000 (major)?

- We have clarified the introduction on page 2 to explain our objective of reviewing studies that either compare CCR to AHA 2000 Guidelines or AHA/ERC 2005 Guidelines to AHA/ERC 2000 Guidelines. It now states: “This is the first systematic review and meta-analysis of the literature to examine the OHCA survival impact of EMS transitions from use of AHA/ERC 2000 Guidelines to use of a CCR protocol or AHA/ERC 2005 Guidelines.”

4. Also, the sensitivity analyses could be more comprehensive (major), perhaps comment further on many of the points in this review, including the selection process and risk of bias in the included studies.

- We appreciate this comment. Please note that we have made significant changes to the 1st paragraph of the limitations section to more fully address the potential for publication bias on page 9. It now includes the statement: “Finally, although our Funnel Plots did not suggest a significant publication bias, it is possible that unpublished, negative studies were underrepresented in our review.”

5. The discussion is brief and focuses mainly on CCR and a more objective evaluation of all data (i.e. the ALS 2005 guidelines) would improve it (major). This is also reflected in the conclusion, which focuses only on CCR, and in which ALS is not mentioned with a single word. As it is now, the discussion seems to be more of an argumentation for CCR than an objective argumentation of the data (major).

- We have amended the discussion to include further information on the AHA guidelines as well as CCR. We have made significant changes to the sections on main findings & limitations, and have specifically mentioned AHA/ERC 2005 Guidelines in the conclusion section. We have included the sentence, “These changes endorsed by the AHA and ERC 2005 Guidelines have likely contributed heavily to the demonstrated progress in OHCA survival” to the 2nd paragraph of the main findings section, page 8.

- We feel it is important to point out the potential reasons why CCR was associated with a survival benefit, and have attempted to make our discussion more reflective of this. On page 8: “However, the most significant difference between AHA/ERC 2005 Guidelines and CCR protocols is the decision to delay intubation in favor of passive ventilation”

6. The authors only touch briefly on the use of therapeutic hypothermia as a joker. In my opinion, this is an important limitation, if not the most important, when comparing the studies and should be dealt with in detail (major). Hypothermia was introduced as routine therapy during the study period and has been shown to improve survival significantly on its own. Perhaps this alone can account for the difference in survival (major)?

- We agree with this comment that the introduction of therapeutic hypothermia is a
possible limitation to the generalizability of our results, and warrants further explanation. We have added the following text to the limitations section on page 10: “The introduction of therapeutic hypothermia represents another important possible limitation to the interpretation of these results. The use of post-arrest hypothermia was not consistent between “control” and “study” protocols of individual studies. Four of the nine studies using AHA 2005 Guidelines reported significantly increased use of therapeutic hypothermia during the “study” protocol period (two other studies did not mention change in hypothermia use). Given the strong evidence for the benefit of therapeutic hypothermia, it is thus likely that the use of hypothermia contributed to the overall trend towards improved survival; our analysis is limited in its ability to calculate the magnitude of that contribution. However, therapeutic hypothermia was not used on any of the patients included in the three CCR studies. Thus, it is extremely unlikely that hypothermia alone could be an alternative explanation for the increase in survival demonstrated by use of the CCR protocols.”

7. Also, in the limitations, the authors touch briefly on confounding in the included studies. This is a highly important subject when only including observational studies and should be covered in a very detailed manor (major).

We have addressed this comment by revising the limitations section on page 9 and 10 to include: “All of the included studies report data from observational studies; no randomized-controlled trials were found that met inclusion criteria, and thus this review was unable to locate studies of the highest scientific quality. Indeed, randomization of OHCA patients to different EMS protocols is impractical and ethically problematic. All of the observational studies included in this review were found to be of high or medium methodological quality based on the NOS, but due to inherent weaknesses in observational studies there exists the potential for confounding and bias within these studies. These potential confounders may include a number of possible changes to the emergency health care systems that occurred between the “control” and “study” protocols, such as community education or improved quality of chest compressions by EMS. Additionally, it is possible that the survival improvement demonstrated here with newer protocols is confounded by temporal changes in the communities studied. Changes in community demographics or disease burden that occurred between and within the periods of data collection could have contributed to the observed changes in survival. However, given the overall similarity in demographics and characteristics of the “control” and “study” subjects (as reported in the individual studies) this potential confounding is not likely to have had a significant influence on the overall results.”

8. In the meta-analysis, some of the numbers used for calculation are very small. For example, only four patients survive to hospital discharge in the AHA 2000 cohort in the study by Bobrow et al. I believe this should be reflected in the discussion (major).

We have amended the limitations section on page 9 to state: “Additionally, some
of the included studies reported few total patients surviving to hospital discharge, and thus were not as heavily weighted in the meta-analysis. However, even with a small number of studies and total subjects, this meta-analysis was sufficiently powered to demonstrate a significant survival benefit.”

9. Also, in the study by Bobrow et al. it was allowed to ventilate the patients. This is an important deviation from the other CCR studies, and an area that I think warrants a thorough discussion (major).

We agree with the reviewer that this is an important point. We have included a discussion of this issue at two separate points in the manuscript. First, in the 4th paragraph of the discussion on page 8: “The benefit of passive insufflation was recently shown in a sub-analysis of the “minimally interrupted cardiac resuscitation” protocol used in Arizona and included in this meta-analysis through Bobrow et al. (2008). Due to reluctance of EMS teams to forgo active ventilation, this protocol allowed airway management through either passive insufflation or bag-valve-mask ventilation, at the discretion of the paramedics.”

Secondly, in the final paragraph of the limitations section on page 10-11, we discuss the differences among studies in strategies for airway management: “Although delayed intubation is one of the pillars of Cardiocerebral Resuscitation, the three studies included in the “AHA 2000 as compared to CCR” group all utilized different protocols for airway management during the “study” protocol time period. The Kansas City Missouri (KCMO) protocol used in Garza et al. (2009) used a 50:2 compression to ventilation ratio. Kellum et al. (2010) delayed intubation for patients with shockable rhythms only. Most significantly, Bobrow et al. (2008) allowed bag-valve-mask ventilation at the paramedics’ discretion. The differences in the airway management strategies of these three studies makes it more difficult to assess which aspects of the CCR protocol contributed most to increased survival, and limits the generalizability of our results.”

Minor Points:

1. Also, I’m not quite sure why the authors have combined a review of CCR and the 2005 guidelines. These are two different approaches to resuscitation and, in my opinion, this could be examined in two separate reviews (minor).

We appreciate this comment, however because the studies of both AHA/ERC 2005 and CCR guidelines are similar, we feel that it is best to include both guidelines into one paper. We feel that this strengthens the reader’s understanding of the different guidelines and their impact on survival.

2. The methods used for the study are up-to-date. The review methodology is clearly stated and reproduction is possible. The study complies with the MOOSE checklist, but there is no search for unpublished studies and thus an increased risk of publication bias (minor).

We have attempted to search for unpublished studies by searching through
abstracts of major conferences, as well as consulting with experts in the field to identify any unpublished studies. In addition, we have conducted two forest plots (Supplemental Figures 1 & 2, shown below) to address publication bias. Based on these two plots, our meta-analysis does not have significant publication bias.

Supplemental Figure 1: Funnel Plot of CCR vs. AHA 2000 Studies

Supplemental Figure 2: Funnel Plot of AHA/ERC 2005 vs. AHA/ERC 2000 Studies

3. The exact methods used in the individual CCR articles are not complete alike, but they seem to be coordinated enough to make the use of meta-analysis valid (minor).

We agree with this comment by the reviewer. Recognizing the differences between the CCR protocols, we set a-priori criteria for defining a protocol as CCR, as stated in the 3rd paragraph of the Inclusion Criteria section on page 4: “We defined an EMS study protocol to be a Cardiocerebral Resuscitation protocol if it contained four out of five critical elements: 1) 200 chest compressions upon initial EMS arrival, 2) if indicated, administration of a single, direct shock, 3) immediate post-shock 200 chest compressions, 4) delayed..."
intubation until after 3 full cycles, and 5) administration of epinephrine as soon as possible.”

Additionally, we have addressed the specific differences between the CCR protocols – in airway management especially – in the limitations section on page 10-11: Although delayed intubation is one of the pillars of Cardiopulmonary Resuscitation, the three studies included in the “AHA 2000 as compared to CCR” group all utilized different protocols for airway management during the “study” protocol time period.

4. Perhaps it would be a good idea to include the ERC guidelines in table 1 to increase comparability (minor).

We have included the ERC 2000 and 2005 guidelines in Table 1. We also state in the introduction on page 2, that “Although the AHA Guidelines have several minor differences from the ERC Guidelines, we considered them similar enough in their strategies for ventilations, compressions, and defibrillations to be grouped together for the purposes of this review.”

5. In the discussion in general, there is a tendency towards a focus on US conditions and not on an international perspective on resuscitation. This is interesting as about 1/3 of all included studies are from outside the US (minor).

We appreciate this reviewer’s comment. By referencing the AHA/ERC Guidelines throughout our discussion, we have attempted to be more general and international in our discussion. We have stated on page 8, “These changes endorsed by the AHA and ERC 2005 Guidelines have likely contributed heavily to the demonstrated progress in OHCA survival” and also on page 11, “The results of this systematic review and meta-analysis demonstrate an association with survival from OHCA when CCR protocols or AHA/ERC 2005 Guidelines are compared to AHA/ERC 2000 Guidelines.”

7. In the entire text, the authors rarely mention to ERC guidelines, even though two studies compare to these. This should be corrected (minor).

We have amended the manuscript to reflect this.

8. The heterogeneity of the 2005 guidelines studies suggests that perhaps these should be analyzed in a different fashion. Perhaps the authors could comment on this (minor)?

We agree that the studies using AHA/ERC 2005 Guidelines have significant heterogeneity. For this reason, we have decided not to attempt an analysis of pooled data on these studies, as explained on page 7: “Although the overall trend was towards a survival benefit for AHA/ERC 2005 Guidelines, heterogeneity tests revealed significant heterogeneity among these nine studies (I² = 72%, p=0.0004), so a pooled odds ratio for survival was not calculated.”

Additionally, we have further discussed the heterogeneity of these studies in the limitations section, page 10: “The heterogeneity of the nine studies using AHA 2005 or ERC 2005 guidelines precluded pooling of their data and a summary
9. Also, it should be noted that Prof. Ewy is a co-author on two of the three CCR studies included in the meta-analysis (minor).

Because Dr. Ewy is a leader in the field of resuscitation science, he has been included in the research team. We understand the reviewer’s concern for possible bias, however we have conducted a systematic and rigorous review of the literature and feel that our results are unbiased and based on the available evidence.

10. In figure 1 between stage 1 and stage 2, have only 191 abstracts been excluded? The authors have reviewed 681 citations, but only 100 are selected for secondary review. 681-100 is more than 191 (minor).

We appreciate the reviewer pointing out this inconsistency. We have revised Figure 1 to accurately reflect that 581 citations were excluded in Stage 1 (from 681 initial citations to 100 abstracts).

11. When reviewing the ALS guidelines, the authors have included the study by Steinmetz et al. even though this includes the use of a mechanical devise. Why have this study been included when the methods section states that studies comparing mechanical devises have been excluded (minor)?

As explained in the 2nd paragraph in the inclusion criteria section on page 3-4, we have excluded studies focusing on mechanical devices: “We excluded reviews, editorials, opinions, studies on bystander resuscitation, studies comparing the absence/presence of advanced life support, studies focusing on mechanical devices, and studies available only as meeting abstracts.” Even though Steinmetz et al. used an AutoPulse device as part of their protocol, we included it in the review because the AutoPulse device was not the focus of the protocol nor the study. Additionally, we have commented on this heterogeneity in the limitations section, page 10: “For example, both the “control” and “study” protocols of Sayre et al. (2009) utilized 2 minutes of CPR prior to first defibrillation attempt, and Steinmetz et al. (2009) utilized a mechanical compression device.”

12. Table 2 would improve by stating whether the different studies were performed retrospectively or prospectively (minor).

All of the studies included in this review were observational studies. All 12 included studies collected data “prospectively” as the OHCAs occurred. A pre/post data analysis was conducted to examine the association between survival and guideline implementation. We have amended the results section on page 5 to further illustrate this: “All 12 articles that were included were prospective observational studies with data on survival pre- and post-implementation of guidelines.”

13. In the abstract, the authors do not state what treatment according to the CCR and ALS 2005 guidelines are compared to in the objective. Other than that, the abstract is clear and

estimate of effect.”
To be more clear, we have modified the abstract on page 1: “To determine if use of Cardiocerebral Resuscitation (CCR) or AHA/ERC 2005 resuscitation guidelines improved patient outcomes from Out-of-Hospital Cardiac Arrest (OHCA) compared to older guidelines.”

14. I haven’t been able to locate a “What this study adds” box (minor).

Indeed, this was not included in our manuscript submission, as it was not specified in the manuscript criteria. For our submission to BMJ Open, we have created an “Article Summary” box for this article, shown below:

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**Article summary:**

**Article focus**

**Key Messages**
- Twelve observational studies on the topic were found, including three studies in which Cardiocerebral Resuscitation was used.
- When AHA/ERC 2005 Guidelines were compared to AHA/ERC 2000 Guidelines, use of the newer guidelines showed an overall trend towards improved survival.
- Cardiocerebral Resuscitation was associated with a significant survival benefit (OR=2.26) compared to older guidelines, including a three-fold increase in survival for patients with a witnessed VF/VT arrest.

**Strengths and limitations of this study**
- This is the first systematic review and meta-analysis of the current evidence on the use of Cardiocerebral Resuscitation and updated AHA/ERC guidelines.
- Only observational studies could be found and reported in this review.
- Significant heterogeneity existed among the included studies in exact resuscitation and treatment protocols, limiting the pooling of data and comparisons between studies.
Use of Cardiocerebral Resuscitation or AHA/ERC 2005 Guidelines Is Associated With Improved Survival from Out-of-Hospital Cardiac Arrest: A Systematic Review & Meta-Analysis

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Use of Cardiocerebral Resuscitation or AHA/ERC 2005 Guidelines Is Associated With Improved Survival from Out-of-Hospital Cardiac Arrest: A Systematic Review & Meta-Analysis

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Keywords:
- Resuscitation
- Cardiac Arrest
- Emergency Medical Services
- Cardiocerebral

Word Count: 4215
Abstract

Objective: To determine if use of Cardiocerebral Resuscitation (CCR) or AHA/ERC 2005 resuscitation guidelines improved patient outcomes from Out-of-Hospital Cardiac Arrest (OHCA) compared to older guidelines.

Design: Systematic review and meta-analysis

Data Sources: MEDLINE, EMBASE, Web of Science, and the Cochrane Library databases. We also hand-searched study references and consulted experts.

Study Selection: Design: randomized controlled trials and observational studies
Population: OHCA patients, age >17 years.
Outcome: Survival to hospital discharge
Quality: High or medium quality studies, as measured by the Newcastle Ottawa Scale (NOS) using pre-defined categories.

Results: Twelve observational studies met inclusion criteria. All 3 studies using CCR demonstrated significantly improved survival compared to use of AHA 2000 guidelines, as did 5 out of the 9 studies using AHA/ERC 2005 Guidelines. Pooled data demonstrates that use of a CCR protocol has an unadjusted Odds Ratio of 2.26 (95% Confidence Interval [CI]: 1.64-3.12) for survival to hospital discharge among all cardiac arrest patients. Among witnessed VF/VT patients, CCR increased survival by an OR of 2.98 (95% CI: 1.92–4.62). Studies using AHA/ERC 2005 Guidelines showed an overall trend towards increased survival, but significant heterogeneity existed among these studies.

Conclusions: We demonstrate an association with improved survival from OHCA when Cardiocerebral Resuscitation protocols or AHA/ERC 2005 Guidelines are compared to use of older guidelines. In the subgroup of patients with witnessed VF/VT, there was a three-fold increase in OHCA survival when CCR was used. CCR appears to be a promising resuscitation protocol for EMS providers in increasing survival from OHCA. Future research will need to be conducted to directly compare AHA/ERC 2010 guidelines with the CCR approach.
Introduction

Out-of-hospital cardiac arrest (OHCA) is a major cause of global mortality and a significant public health concern. In the US alone, an estimated 300,000 people suffer an OHCA each year, and only 7% will survive to hospital discharge.1 The survival rate had previously remained unchanged for over three decades despite a dramatic increase in our understanding of OHCA and its predictors of survival.2

International standards for the emergency treatment of OHCA have existed since 1966, and the American Heart Association (AHA) published its first set of formal guidelines for CPR in 1992.3-4 Updates to the AHA and European Resuscitation Council (ERC) Guidelines in 2000 and 2005 reflected, in large part, a growing understanding of the electrophysiological phases of cardiac arrest and the need to minimize interruptions in chest compressions.5-6 Concurrently, animal and human studies have indicated that active ventilation during resuscitation may be unnecessary, and even detrimental.7-8 This has lead to the development of a new body of EMS (Emergency Medical Services) resuscitation protocols that minimize ventilation and maximize the amount of time spent by EMS doing chest compressions. One such protocol is Cardiocerebral Resuscitation (CCR), which emphasizes passive ventilation, continuous chest compressions, and delayed intubation. CCR was first instituted in 2003 as an alternative resuscitation protocol due to poor survival rates observed using the standard guidelines.9-10 At the time, CCR represented a significant departure from the AHA 2000 Guidelines because of its use of a single defibrillator shock instead of triple stacked shocks. This key resuscitation element was later incorporated into AHA and ERC 2005 Guidelines, and CCR has since shown promise in improving survival from OHCA.11-12

While a majority of EMS systems continue to use AHA or ERC-based guidelines for CPR, a growing number have adopted the CCR protocol. To date, no systematic review has been conducted to compare standard AHA/ERC Guidelines to CCR protocols. Although the AHA Guidelines have several minor differences from the ERC Guidelines, we considered them similar enough in their strategies for ventilations, compressions, and defibrillations to be grouped together for the purposes of this review. This is the first systematic review and meta-analysis of the literature to examine the OHCA survival impact of EMS transitions from use of AHA/ERC 2000 Guidelines to use of a CCR protocol or AHA/ERC 2005 Guidelines.
Methods

This systematic review and meta-analysis was performed according to guidelines set forth by the MOOSE (Meta-Analysis Of Observational Studies in Epidemiology) checklist. Planning and study design were done by two authors (MS, CS), and included creation of an electronic database (Microsoft Excel) with defined primary endpoints and variables of interest that can be obtained from study authors on request.

Search strategy

A search was conducted of the following databases: MEDLINE (Ovid) (via PubMed), 1950 to Dec 2011; EMBASE (Ovid), 1966 to 2011; Web of Science, 1970 to 2011; the Cochrane Central Register of Controlled Trials; the Cochrane Database of Systematic Reviews; the Database of Abstracts of Reviews of Effects; the NHS Economic Evaluation Database; and the Health Technology Assessment Database. Our search strategy included searching for keywords such as “cardiocerebral”, “minimally interrupted”, and “continuous compressions” (using truncation and adjacency techniques) from within the subject headings of “Heart Arrest”, “Resuscitation”, and “Emergency Medical Services”. Results were limited to human studies with English abstracts published since 2000. The full details of all the search strategies can be obtained from study authors on request. Additionally, we reviewed the bibliographies of included studies and published review articles, as well as sought expert opinion (GE) to obtain additional studies. The search included all through December 1, 2011.

Inclusion criteria

Studies were considered eligible for inclusion if they met criteria for study design, control protocol, study protocol, outcome, and methodological quality (Box 1). Similar to other recent studies, methodological quality was assessed using the Newcastle Ottawa Scale (NOS) for cohort studies, wherein studies are given up to nine total points for fulfilling criteria in Selection, Comparability, & Exposure. We categorized studies as high quality if they received eight or nine points, medium quality if they received six or seven points, and low quality if they received five points or less. Only high and medium quality studies were included in this review.
We excluded reviews, editorials, opinions, studies on bystander resuscitation, studies comparing the absence/presence of advanced life support, studies focusing on mechanical devices, and studies available only as meeting abstracts. In addition, we excluded studies with non-English language full-text, studies meeting incomplete criteria for the resuscitation protocols, and studies containing duplicative data of the included studies.

To be considered for inclusion, studies must have explicitly stated use of AHA 2000 Guidelines or ERC 2000 Guidelines as their EMS “control” protocol. These studies had to directly compare EMS use of AHA 2000/ERC 2000 guidelines to either AHA 2005, ERC 2005, or CCR protocols. Cardiocerebral Resuscitation has several distinct and important differences from the AHA and ERC Guidelines for cardiopulmonary resuscitation, which are illustrated in Table 1. We defined an EMS study protocol to be a Cardiocerebral Resuscitation protocol if it contained four out of five critical elements12: 1) 200 chest compressions upon initial EMS arrival, 2) if indicated, administration of a single, direct shock, 3) immediate post-shock 200 chest compressions, 4) delayed intubation until after 3 full cycles, and 5) administration of epinephrine as soon as possible.

Study selection process

We screened citations in three stages (Figure 1). In Stage 1, one reviewer (MS) reviewed all citations by title or abstract to exclude clearly irrelevant and duplicate citations. In Stage 2, two reviewers (MS, CS) screened remaining abstracts for potential inclusion. In Stage 3, three reviewers (MS, CS, GE) reviewed the full text of all potentially eligible studies, and final inclusion was based on the agreement of all three investigators. Reviewers were not blinded to study authors or outcomes.

Data Extraction

Relevant information from the studies, including characteristics of the study population and outcome measures, was extracted by two reviewers (MS, CS) using the prepared extraction database (Microsoft Excel). Data on study characteristics (year, location), variables of interest (age, gender, witnessed arrest, bystander CPR, initial shockable rhythm, EMS response time), total patient numbers per group, and outcomes of relevant groups were extracted. When included, data was extracted directly from Utstein templates. Absolute numbers were recalculated when percentages were reported.
Data Analysis & Synthesis

Individual study data were used to calculate unadjusted odds ratios (OR) for survival to hospital discharge for each EMS “control” and EMS “study” (defined as either AHA 2005 or CCR) protocol. Outcome data of the included studies were combined within each group to estimate the pooled effect (odds ratio, OR) for the use of CCR compared to AHA 2000 and the use of AHA 2005 compared to AHA 2000. Because witnessed ventricular fibrillation is a commonly used measure of OHCA survival, we conducted a subgroup analysis of these patients to compare the control versus study protocols for AHA 2005 and CCR guidelines. Calculations were based on a DerSimonian and Laird random effects model.16 Heterogeneity among trials was quantified with Higgins’s and Thompson’s I2, which can be interpreted as the percentage of variability due to heterogeneity between studies rather than sampling error. Publication bias was assessed by generating separate Funnel Plots for each of the two groups of studies. Findings are presented as point estimates and 95% confidence intervals, and when appropriate, weight of individual studies. All analyses were performed within RevMan version 5.1.17

Results

Identification and selection of studies

Our initial electronic search yielded 654 citations, and an additional 27 were identified through hand-search of bibliographies and other sources. After an initial screen of titles, 100 abstracts were reviewed, and 22 of those were subsequently selected for full-text review. Six studies were excluded for lacking sufficient number of CCR elements, three studies excluded for sharing duplicative data with included studies, and one study for non-English language text. Finally, 12 total studies satisfied the predetermined inclusion criteria: three using Cardiocerebral Resuscitation and nine using AHA 2005 or ERC 2005 Guidelines, as shown in Figure 1.

Characteristics of included studies

The final sample included 12 studies, with approximately 19,634 subjects. Study characteristics and pertinent outcome data are shown in Table 2. All 12 articles that were included were prospective observational studies with data on survival pre- and post-
implementation of guidelines. Eight of the 12 studies were rated as high quality, and four were rated as medium quality. No randomized controlled trials were identified that met inclusion criteria.

Three studies, which included a total of 2,820 subjects, met the predetermined criteria for use of AHA 2000 (control) versus CCR (study) protocol.\textsuperscript{18-20} Nine studies, which included a total of 16,814 subjects, compared the use of AHA 2000/ERC 2000 (control) versus AHA 2005/ERC 2005 (study) protocols.\textsuperscript{21-29}

Eight of the studies were conducted in North America, and one each in Taiwan, Norway, New Zealand, and Denmark. Data on EMS control protocols (2000 Guidelines) were collected in the range of 2003 to 2006, except for Kellum (2008) which began collecting data in 2001. Data on EMS study protocols (CCR or AHA/ERC 2005 Guidelines) were collected in the range of 2004 to 2008. Of note, none of the studies using CCR, but five of studies using AHA 2005 Guidelines explicitly reported consistent use of therapeutic hypothermia during the study period.\textsuperscript{21 23 25 26 28}

The mean subject age across all studies was 64 years, and the mean gender distribution was 66.4% male. Two studies had significant differences in age between their control and study populations.\textsuperscript{22 25}

There was a wide range across studies in the proportion of OHCA receiving bystander CPR (8% to 58%) with a mean of 34.6%. The mean EMS response time was 6.2 minutes, with a range of 4.7 to 9.3 minutes. The mean proportion of OHCA patients with a presenting rhythm of ventricular fibrillation or ventricular tachycardia was 29.9%, with a range of 5.6% to 50%. Three studies reported statistically significant differences in the proportion of witnessed arrest, proportion of bystander-CPR, or response time between control and study populations.\textsuperscript{20 22 23}

**Overall Outcomes**

Survival to hospital discharge was identified as the primary or secondary outcome in all studies. Mean survival when using AHA/ERC 2000 Guidelines was 6.9% (range of 1.8% to 11.1%). Mean survival to discharge increased to 10.1% (6.5% - 19.4%) when using AHA/ERC 2005 Guidelines, and to 9.3% (5.4% to 18.3%) when Cardiocerebral Resuscitation was used. Overall mean survival across all studies and protocols was 9.7%.

**AHA 2000 Guidelines as compared to CCR**
All three of the studies using a CCR protocol showed significantly improved survival for CCR compared to use of AHA 2000 Guidelines. Pooled analysis of data from these studies (Figure 2) demonstrated a statistically significant survival benefit when using a CCR protocol, with a pooled odds ratio of 2.26 (95% CI: 1.64 – 3.12). Heterogeneity among the studies was not significant ($I^2 = 0.0\%$, $p=0.61$).

Subgroup analysis of the patients with a presenting rhythm of witnessed ventricular fibrillation/ventricular tachycardia showed a significant association with survival for the CCR protocol as compared to the AHA 2000 Guidelines. Pooled odds ratio of survival to hospital discharge for this subgroup was 2.98 (95% CI: 1.92 – 4.62) (Figure 2). The funnel plot of these three studies was not suggestive of publication bias (Supplemental Figure 1).

AHA/ERC 2000 Guidelines as compared to AHA/ERC 2005 Guidelines

Eight of the nine studies using AHA/ERC 2005 Guidelines demonstrated improved survival to hospital discharge for use of AHA/ERC 2005 compared to AHA/ERC 2000 guidelines, a result that was statistically significant in five out of nine studies (Figure 3). Although the overall trend was towards a survival benefit for AHA/ERC 2005 Guidelines, heterogeneity tests revealed significant heterogeneity among these nine studies ($I^2 = 72\%$, $p=0.0004$), so a pooled odds ratio for survival was not calculated.\textsuperscript{30}

Subgroup analysis of the patients with a presenting rhythm of witnessed ventricular fibrillation/ventricular tachycardia showed a trend toward improved survival for the AHA/ERC 2005 Guidelines as compared to the AHA/ERC 2000 Guidelines. However, there was significant heterogeneity between studies so a pooled odds ratio was not calculated.\textsuperscript{30} The funnel plot of these nine studies was not suggestive of publication bias (Supplemental Figure 2).

**Discussion**

**Main Findings**

In our systematic review of 12 studies and 19,634 subjects, we found a consistent and significant survival benefit from out-of-hospital cardiac arrest when EMS transitioned to use of updated resuscitation protocols. Our meta-analysis findings suggest that, compared to AHA 2000 Guidelines, use of CCR has a significant association with increased survival for all OHCA patients. In our subgroup analysis of patients with a presenting rhythm of VF/VT, use of a CCR protocol was associated with nearly a 3-fold increase in survival. This association was not as
clear in the comparison of the AHA/ERC 2000 to AHA/ERC 2005 Guidelines, as there was a trend toward improved survival, but a pooled odds ratio could not be calculated secondary to heterogeneity between studies. Although a pooled estimate of effect was not possible for this set of studies, the 2005 updates to resuscitation guidelines appear to have led to a demonstrable effect on OHCA survival.

It appears that both the CCR protocols and AHA/ERC 2005 Guidelines are associated with overall increases in survival from OHCA. After years of unchanged survival rates, this is a promising new finding. Furthermore, the association with improved survival is seen most clearly in the studies using a CCR protocol. Based on animal models and human studies, it is likely that multiple elements of the AHA/ERC 2005 Guidelines and CCR protocols have contributed to this progress. Both the AHA/ERC 2005 Guidelines and CCR emphasize the need to maintain coronary and cerebral perfusion pressure by minimizing interruptions in chest compressions, although CCR eliminates any stoppage for ventilations. The benefits of this emphasis on optimal chest compression depth and continuous rate of chest compressions have been shown in multiple animal studies.31-32 In addition, both protocols emphasize 150-200 compressions immediately prior and immediately after defibrillation attempts, in recognition of the evidence that a perfused heart is much more likely to convert to a pulsatile rhythm after shock.33-37 These changes endorsed by the AHA and ERC 2005 Guidelines have likely contributed heavily to the demonstrated progress in OHCA survival.

However, the most significant difference between AHA/ERC 2005 Guidelines and CCR protocols is the decision to delay intubation in favor of passive ventilation. An existing body of studies has shown that intubations can 1) cause significant delays and/or interruptions in chest compressions38, and 2) lead to excessive positive pressure ventilation which can reduce venous return, reduce cerebral and coronary perfusion pressures, and consequently reduce likelihood of survival.7-8

The benefit of passive insufflation was recently shown in a sub-analysis of the “minimally interrupted cardiac resuscitation” protocol used in Arizona and included in this meta-analysis through Bobrow et al. (2008).39 Due to reluctance of EMS teams to forgo active ventilation, this protocol allowed airway management through either passive insufflation or bag-valve-mask ventilation, at the discretion of the paramedics. For the subset of patients most likely to survive (witnessed VF/VT), neurologically intact survival was significantly higher among patients who received passive insufflation only as compared to bag-valve mask (38.2% compared to 25.8%).39
Another study, published in 2011, showed an association with increased survival when a non-standard resuscitation protocol was implemented in Sussex County, United Kingdom.\textsuperscript{40} Delayed ventilation was a key feature in this protocol; patients with witnessed OHCA and initial VF/VT were not given any active ventilations until after three cycles of 100 compressions plus shock. Using this strategy, survival in these patients increased from a historical baseline of 13% to approximately 30%.\textsuperscript{40}

The newest ERC and AHA Guidelines were recently released in late-2010.\textsuperscript{41-42} The ERC Guidelines have removed the recommendation for a specified period of CPR prior to first defibrillation, while the AHA Guidelines have a strong emphasis on C-A-B: compressions, airway and then breathing. The shift to focusing on providing quality chest compression at a rate of at least 100 per minute is a change from the AHA 2000 and 2005 guidelines in which the airway and breathing were first addressed. Although this is similar to the approach to CCR, there are still significant differences, the most significant being that CCR encourages compressions without ventilations. Future research will need to be conducted to directly compare survival between use of the updated AHA and ERC 2010 Guidelines and use of CCR.

Limitations:

This systematic review yielded a total of 12 studies reporting results on CCR and AHA/ERC 2005 Guidelines as compared to AHA/ERC 2000 Guidelines. This relatively small sample limits the generalizability of our results in several ways. Only three studies reported results from the use of CCR protocols, which limited the meta-analysis to include only 2820 total subjects. Additionally, some of the included studies reported few total patients surviving to hospital discharge, and thus were not as heavily weighted in the meta-analysis. However, even with a small number of studies and total subjects, this meta-analysis was sufficiently powered to demonstrate a significant survival benefit. Finally, although our Funnel Plots did not suggest a significant publication bias, it is possible that unpublished, negative studies were underrepresented in our review. Future research from multiple research centers across the U.S. and internationally could potentially strengthen the results demonstrated here.

All of the included studies report data from observational studies; no randomized-controlled trials were found that met inclusion criteria, and thus this review was unable to locate studies of the highest scientific quality. Indeed, randomization of OHCA patients to different EMS protocols is impractical and ethically problematic. All of the observational studies included in
this review were found to be of high or medium methodological quality based on the NOS, but due to inherent weaknesses in observational studies there exists the potential for confounding and bias within these studies. The combination of multiple observational studies into a meta-analysis has the potential limitation of masking confounders that exist within the individual studies. These confounders may include a number of unrecognized variables of cardiac resuscitation, as well as possible changes made to the emergency health care systems between the “control” and “study” protocols, such as community education or improved quality of chest compressions by EMS. Additionally, it is possible that the survival improvement demonstrated here with newer protocols is confounded by temporal changes in the communities studied. Changes in community demographics or disease burden that occurred between and within the periods of data collection could have contributed to the observed changes in survival. The overall similarity in demographics and characteristics of the “control” and “study” subjects (as reported in the individual studies) makes it unlikely that this potential confounder has had a significant influence on our overall results. However, the existence of other, unrecognized confounders of the individual studies remains an important limitation to our meta-analysis.

The introduction of therapeutic hypothermia represents another important possible limitation to the interpretation of these results. The use of post-arrest hypothermia was not consistent between “control” and “study” protocols of individual studies. Four of the nine studies using AHA 2005 Guidelines reported significantly increased use of therapeutic hypothermia during the “study” protocol period (two other studies did not mention change in hypothermia use). Given the strong evidence for the benefit of therapeutic hypothermia\textsuperscript{43-44}, it is thus likely that the use of hypothermia contributed to the overall trend towards improved survival; our analysis is limited in its ability to calculate the magnitude of that contribution. However, therapeutic hypothermia was not used on any of the patients included in the three CCR studies. Thus, it is extremely unlikely that hypothermia alone could be an alternative explanation for the increase in survival demonstrated by use of the CCR protocols.

The heterogeneity of the nine studies using AHA 2005 or ERC 2005 guidelines precluded pooling of their data and a summary estimate of effect. These studies were also heterogeneous in the specifics of the resuscitation protocols used, many employing minor deviations from the AHA or ERC guidelines. For example, both the “control” and “study” protocols of Sayre et al. (2009) utilized 2 minutes of CPR prior to first defibrillation attempt, and Steinmetz et al. (2009) utilized a mechanical compression device. Additionally, there exist minor but important
differences between the AHA and ERC resuscitation guidelines. While these variations might have influenced the results of the individual studies, the random-effects model used for our pooled data analysis accounted for some of this variability. Still these variations serve to highlight the difficulty of standardizing resuscitation protocols and comparing EMS systems.

Although delayed intubation is one of the pillars of Cardiocerebral Resuscitation, the three studies included in the “AHA 2000 as compared to CCR” group all utilized different protocols for airway management during the “study” protocol time period. The Kansas City Missouri (KCMO) protocol used in Garza et al. (2009) used a 50:2 compression to ventilation ratio. Kellum et al. (2010) delayed intubation for patients with shockable rhythms only. Most significantly, Bobrow et al. (2008) allowed bag-valve-mask ventilation at the paramedics’ discretion. The differences in the airway management strategies of these three studies makes it more difficult to assess which aspects of the CCR protocol contributed most to increased survival, and limits the generalizability of our results.

Conclusions:

The results of this systematic review and meta-analysis demonstrate an association with survival from OHCA when CCR protocols or AHA/ERC 2005 Guidelines are compared to AHA/ERC 2000 Guidelines. Although no randomized trials have yet been reported, multiple high quality observational studies have demonstrated an association with increased survival post-AHA/ERC 2005 guideline or CCR implementation. Additionally, in the pooled subgroup of witnessed VF/VT patients, there was a three-fold increase in OHCA survival after a CCR protocol was implemented. The focus of the updated AHA 2010 and ERC 2010 Guidelines shifts emphasis toward providing uninterrupted, quality chest compressions. However these changes still do not incorporate key elements of the CCR protocol that this study indicates are associated with improved OHCA survival, such as passive insufflation and minimal interruptions of chest compressions. Our study suggests that CCR appears to be a promising resuscitation protocol for EMS providers in increasing survival from OHCA. Future research will need to be conducted to directly compare AHA/ERC 2010 Guidelines with the CCR approach.

Authors’ contributions: MS, CS conceptualized and designed this systematic review and meta-analysis. MS, CS were substantially involved in data acquisition (literature search, study selection, and data abstraction). MS, CS performed the analyses and were substantially involved in data interpretation. MS, GE, CS provided data used for the analysis and relevantly contributed to the interpretation and intellectual content of the manuscript. MS, CS drafted the
manuscript. All authors revised the manuscript critically for important intellectual content. All authors approved the final version.

Funding: This project received no specific funding

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work

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Ethical approval: not required

Data sharing: available from authors upon request

Box: Inclusion criteria for eligible studies

Study Design: Randomized controlled trials and observational studies

Population: Out-of-Hospital Cardiac Arrest patients, >17 years of age.


EMS Study Protocol: AHA 2005 Guidelines or ERC 2005 Guidelines for Cardiopulmonary Resuscitation, or Cardiocerebral Resuscitation

Outcomes: Rate of bystander CPR, EMS response time, Proportion of initial VF/VT, and Survival to hospital discharge

Quality: High or Medium quality, as categorized using the Newcastle Ottawa Scale (NOS) for cohort studies.
### Table 1: AHA vs ERC vs CCR Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Compressions</th>
<th>Ventilation</th>
<th>Defibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AHA 2000 CPR</strong></td>
<td>15:2 ratio</td>
<td><em>Tracheal Intubation</em></td>
<td>Pre: ---</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10-12 breaths/min</td>
<td><em>Triple Shock</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Pulse Check</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post: 1 min CPR</td>
</tr>
<tr>
<td><strong>ERC 2000 CPR</strong></td>
<td>15:2 ratio</td>
<td><em>Tracheal Intubation</em></td>
<td>Pre: ---</td>
</tr>
<tr>
<td></td>
<td></td>
<td>~12 breaths/min</td>
<td><em>Triple Shock</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Pulse Check</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post: 1 min CPR</td>
</tr>
<tr>
<td><strong>AHA 2005 CPR</strong></td>
<td>30:2 ratio</td>
<td><em>Tracheal Intubation</em></td>
<td>Pre: Optional 5 cyc</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8-10 breaths/min</td>
<td><em>Single Shock</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Pulse Check</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post: 5 cycles</td>
</tr>
<tr>
<td><strong>ERC 2005 CPR</strong></td>
<td>30:2 ratio</td>
<td><em>Tracheal Intubation</em></td>
<td>Pre: 2 min CPR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8-10 breaths/min</td>
<td><em>Single Shock</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Pulse Check</em></td>
</tr>
<tr>
<td><strong>Cardiocerebral</strong></td>
<td>Continuous</td>
<td><em>Passive Only; Delayed Intubation</em></td>
<td>Pre: 200 compress</td>
</tr>
<tr>
<td><strong>Resuscitation (2003)</strong></td>
<td>100/min</td>
<td></td>
<td><em>Single Shock</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post: 200 compress</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Pulse Check</em></td>
</tr>
</tbody>
</table>
Figure 1: Flow chart depicting the outline of study selection process

654 potentially relevant citations identified through database searching

27 additional citations identified through hand-search of bibliographies and other sources

681 citations screened by title & abstract for potential inclusion

Excluded, n=581
n=581: Reviews, opinions, clear irrelevance, duplicates

Stage 1: Review of title or abstract

100 potential citations for secondary review

Excluded, n=78
n=37: Comment, reviews, Utstein reports
n=20: Bystander CPR/dispatcher CPR
n=10: Only partial elements of CCR
n=4: Focus on EMS ACLS
n=4: Meeting abstracts only
n=3: Mechanical CPR devices

Stage 2: Review of abstract

22 studies comparing AHA 2000, Guidelines to AHA 2005 Guidelines or CCR protocol

Excluded, n=10
n=6: Incomplete criteria for CCR
n=3: Duplicative data of included studies
n=1: Non-English language

Stage 3: Full-text review

3 studies meeting complete CCR criteria

9 studies of AHA guideline changes

Included in Review

Excluded, n=581
n=581: Reviews, opinions, clear irrelevance, duplicates
Table 2: Characteristics and outcomes of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Quality</th>
<th>Control vs. Study Protocol</th>
<th>Bystander CPR (%)</th>
<th>Response Time (min)</th>
<th>Initial VF/VT (%)</th>
<th>Total Arrests (n)</th>
<th>Survival to Discharge (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bobrow (2008)</td>
<td>Arizona</td>
<td>High</td>
<td>AHA 2000</td>
<td>34</td>
<td>5.6</td>
<td>31.7</td>
<td>218</td>
<td>4 (1.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MICR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>39</td>
<td>5.2</td>
<td>29.9</td>
<td>668</td>
<td>36 (5.4%)</td>
</tr>
<tr>
<td>Garza (2009)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Missouri</td>
<td>High</td>
<td>AHA 2000</td>
<td>38</td>
<td>5.4</td>
<td>31.4</td>
<td>1097</td>
<td>64 (5.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>KCMO Protocol&lt;sup&gt;b&lt;/sup&gt;</td>
<td>47</td>
<td>5.3</td>
<td>33.3</td>
<td>339</td>
<td>37 (10.9%)</td>
</tr>
<tr>
<td>Kellum (2008)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Wisconsin</td>
<td>High</td>
<td>AHA 2000</td>
<td>45&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>42.5</td>
<td>268</td>
<td>21 (7.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CCR</td>
<td>45&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>47.4</td>
<td>230</td>
<td>42 (18.3%)</td>
</tr>
<tr>
<td>Auftderheide (2010)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>MN, TX, NE, FL, NC</td>
<td>High</td>
<td>AHA 2000</td>
<td>38</td>
<td>5.6</td>
<td>25.3</td>
<td>1641</td>
<td>166 (10.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AHA 2005</td>
<td>40</td>
<td>5.6</td>
<td>23.9</td>
<td>1605</td>
<td>211 (13.1%)</td>
</tr>
<tr>
<td>Bigham (2011)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Canada &amp;</td>
<td>Medium</td>
<td>AHA 2000</td>
<td>29</td>
<td>5.8</td>
<td>23.1</td>
<td>5054</td>
<td>294 (5.8%)</td>
</tr>
</tbody>
</table>
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Location</th>
<th>Quality</th>
<th>CCR Protocol</th>
<th>AHA 2000 Guidelines</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bobrow (2005)</td>
<td>USA</td>
<td>High</td>
<td>36</td>
<td>668</td>
<td>218</td>
<td>9.5%</td>
</tr>
<tr>
<td>Garza (2009)</td>
<td>USA</td>
<td>High</td>
<td>37</td>
<td>339</td>
<td>64</td>
<td>1097</td>
</tr>
<tr>
<td>Kellum (2008)</td>
<td>USA</td>
<td>High</td>
<td>42</td>
<td>230</td>
<td>21</td>
<td>258</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>USA</td>
<td>High</td>
<td>1237</td>
<td>1583</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>115</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.98$, df = 2 ($P = 0.61$); $I^2 = 0$
| Test for overall effect: $Z = 4.99$ ($P < 0.00001$) |

Figure 2: Forest Plot of Pooled Odds Ratios: CCR vs. AHA 2000 Studies

Figure 3: Forest Plot of Odds Ratios for Witnessed VF/VT Survival: CCR vs. AHA/ERC 2000 Studies

a Minimally Interrupted Cardiac Resuscitation (MICR) allowed either passive insufflation or bag-valve-mask ventilation at paramedic discretion
b Kansas City, Missouri (KCMO) Protocol included a 50:2 compression to ventilation ratio
c These values represent the sub-population of witnessed VF/VT
d Values are reported from “Phase 3” of the step-wise introduction of AHA 2005 guidelines
e These protocols represent the “Pre” and “Post” states of a community intervention
f Both protocols used 2 minutes of CPR prior to the first defibrillation
g This protocol used an automated compression device (AutoPulse™)
h Quality categorized as High, Medium, or Low using the Newcastle Ottawa Scale, similar to other recent meta-analyses.
Figure 4: Forest Plot of Odds Ratios: AHA/ERC 2005 vs. AHA/ERC 2000 Studies

References:


Use of Cardiocerebral Resuscitation or AHA/ERC 2005 Guidelines Is Associated With Improved Survival from Out-of-Hospital Cardiac Arrest: A Systematic Review & Meta-Analysis

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Keywords:
- Resuscitation
- Cardiac Arrest
- Emergency Medical Services
- Cardiocerebral

Word Count: 4215
Abstract

Objective: To determine if use of Cardiocerebral Resuscitation (CCR) or AHA/ERC 2005 resuscitation guidelines improved patient outcomes from Out-of-Hospital Cardiac Arrest (OHCA) compared to older guidelines.

Design: Systematic review and meta-analysis

Data Sources: MEDLINE, EMBASE, Web of Science, and the Cochrane Library databases. We also hand-searched study references and consulted experts.

Study Selection: Design: randomized controlled trials and observational studies
Population: OHCA patients, age >17 years.
Outcome: Survival to hospital discharge
Quality: High or medium quality studies, as measured by the Newcastle Ottawa Scale (NOS) using pre-defined categories.

Results: Twelve observational studies met inclusion criteria. All 3 studies using CCR demonstrated significantly improved survival compared to use of AHA 2000 guidelines, as did 5 out of the 9 studies using AHA/ERC 2005 Guidelines. Pooled data demonstrates that use of a CCR protocol has an unadjusted Odds Ratio of 2.26 (95% Confidence Interval [CI]: 1.64-3.12) for survival to hospital discharge among all cardiac arrest patients. Among witnessed VF/VT patients, CCR increased survival by an OR of 2.98 (95% CI: 1.92–4.62). Studies using AHA/ERC 2005 Guidelines showed an overall trend towards increased survival, but significant heterogeneity existed among these studies.

Conclusions: We demonstrate an association with improved survival from OHCA when Cardiocerebral Resuscitation protocols or AHA/ERC 2005 Guidelines are compared to use of older guidelines. In the subgroup of patients with witnessed VF/VT, there was a three-fold increase in OHCA survival when CCR was used. CCR appears to be a promising resuscitation protocol for EMS providers in increasing survival from OHCA. Future research will need to be conducted to directly compare AHA/ERC 2010 guidelines with the CCR approach.
**Introduction**

Out-of-hospital cardiac arrest (OHCA) is a major cause of global mortality and a significant public health concern. In the US alone, an estimated 300,000 people suffer an OHCA each year, and only 7% will survive to hospital discharge.\(^1\) The survival rate had previously remained unchanged for over three decades despite a dramatic increase in our understanding of OHCA and its predictors of survival.\(^2\)

International standards for the emergency treatment of OHCA have existed since 1966, and the American Heart Association (AHA) published its first set of formal guidelines for CPR in 1992.\(^3\)\(^-\)\(^4\) Updates to the AHA and European Resuscitation Council (ERC) Guidelines in 2000 and 2005 reflected, in large part, a growing understanding of the electrophysiological phases of cardiac arrest and the need to minimize interruptions in chest compressions.\(^5\)\(^-\)\(^6\) Concurrently, animal and human studies have indicated that active ventilation during resuscitation may be unnecessary, and even detrimental.\(^7\)\(^-\)\(^8\) This has lead to the development of a new body of EMS (Emergency Medical Services) resuscitation protocols that minimize ventilation and maximize the amount of time spent by EMS doing chest compressions. One such protocol is Cardiocerebral Resuscitation (CCR), which emphasizes passive ventilation, continuous chest compressions, and delayed intubation. CCR was first instituted in 2003 as an alternative resuscitation protocol due to poor survival rates observed using the standard guidelines.\(^9\)\(^-\)\(^10\) At the time, CCR represented a significant departure from the AHA 2000 Guidelines because of its use of a single defibrillator shock instead of triple stacked shocks. This key resuscitation element was later incorporated into AHA and ERC 2005 Guidelines, and CCR has since shown promise in improving survival from OHCA.\(^11\)\(^-\)\(^12\)

While a majority of EMS systems continue to use AHA or ERC-based guidelines for CPR, a growing number have adopted the CCR protocol. To date, no systematic review has been conducted to compare standard AHA/ERC Guidelines to CCR protocols. Although the AHA Guidelines have several minor differences from the ERC Guidelines, we considered them similar enough in their strategies for ventilations, compressions, and defibrillations to be grouped together for the purposes of this review. This is the first systematic review and meta-analysis of the literature to examine the OHCA survival impact of EMS transitions from use of AHA/ERC 2000 Guidelines to use of a CCR protocol or AHA/ERC 2005 Guidelines.
Methods

This systematic review and meta-analysis was performed according to guidelines set forth by the MOOSE (Meta-Analysis Of Observational Studies in Epidemiology) checklist. Planning and study design were done by two authors (MS, CS), and included creation of an electronic database (Microsoft Excel) with defined primary endpoints and variables of interest that can be obtained from study authors on request.

Search strategy

A search was conducted of the following databases: MEDLINE (Ovid) (via PubMed), 1950 to Dec 2011; EMBASE (Ovid), 1966 to 2011; Web of Science, 1970 to 2011; the Cochrane Central Register of Controlled Trials; the Cochrane Database of Systematic Reviews; the Database of Abstracts of Reviews of Effects; the NHS Economic Evaluation Database; and the Health Technology Assessment Database. Our search strategy included searching for keywords such as “cardiocerebral”, “minimally interrupted”, and “continuous compressions” (using truncation and adjacency techniques) from within the subject headings of “Heart Arrest”, “Resuscitation”, and “Emergency Medical Services”. Results were limited to human studies with English abstracts published since 2000. The full details of all the search strategies can be obtained from study authors on request. Additionally, we reviewed the bibliographies of included studies and published review articles, as well as sought expert opinion (GE) to obtain additional studies. The search included all through December 1, 2011.

Inclusion criteria

Studies were considered eligible for inclusion if they met criteria for study design, control protocol, study protocol, outcome, and methodological quality (Box 1). Similar to other recent studies, methodological quality was assessed using the Newcastle Ottawa Scale (NOS) for cohort studies, wherein studies are given up to nine total points for fulfilling criteria in Selection, Comparability, & Exposure. We categorized studies as high quality if they received eight or nine points, medium quality if they received six or seven points, and low quality if they received five points or less. Only high and medium quality studies were included in this review.
We excluded reviews, editorials, opinions, studies on bystander resuscitation, studies comparing the absence/presence of advanced life support, studies focusing on mechanical devices, and studies available only as meeting abstracts. In addition, we excluded studies with non-English language full-text, studies meeting incomplete criteria for the resuscitation protocols, and studies containing duplicative data of the included studies.

To be considered for inclusion, studies must have explicitly stated use of AHA 2000 Guidelines or ERC 2000 Guidelines as their EMS “control” protocol. These studies had to directly compare EMS use of AHA 2000/ERC 2000 guidelines to either AHA 2005, ERC 2005, or CCR protocols. Cardiocerebral Resuscitation has several distinct and important differences from the AHA and ERC Guidelines for cardiopulmonary resuscitation, which are illustrated in Table 1. We defined an EMS study protocol to be a Cardiocerebral Resuscitation protocol if it contained four out of five critical elements12: 1) 200 chest compressions upon initial EMS arrival, 2) if indicated, administration of a single, direct shock, 3) immediate post-shock 200 chest compressions, 4) delayed intubation until after 3 full cycles, and 5) administration of epinephrine as soon as possible.

Study selection process

We screened citations in three stages (Figure 1). In Stage 1, one reviewer (MS) reviewed all citations by title or abstract to exclude clearly irrelevant and duplicate citations. In Stage 2, two reviewers (MS, CS) screened remaining abstracts for potential inclusion. In Stage 3, three reviewers (MS, CS, GE) reviewed the full text of all potentially eligible studies, and final inclusion was based on the agreement of all three investigators. Reviewers were not blinded to study authors or outcomes.

Data Extraction

Relevant information from the studies, including characteristics of the study population and outcome measures, was extracted by two reviewers (MS, CS) using the prepared extraction database (Microsoft Excel). Data on study characteristics (year, location), variables of interest (age, gender, witnessed arrest, bystander CPR, initial shockable rhythm, EMS response time), total patient numbers per group, and outcomes of relevant groups were extracted. When included, data was extracted directly from Utstein templates. Absolute numbers were recalculated when percentages were reported.
Data Analysis & Synthesis

Individual study data were used to calculate unadjusted odds ratios (OR) for survival to hospital discharge for each EMS “control” and EMS “study” (defined as either AHA 2005 or CCR) protocol. Outcome data of the included studies were combined within each group to estimate the pooled effect (odds ratio, OR) for the use of CCR compared to AHA 2000 and the use of AHA 2005 compared to AHA 2000. Because witnessed ventricular fibrillation is a commonly used measure of OHCA survival, we conducted a subgroup analysis of these patients to compare the control versus study protocols for AHA 2005 and CCR guidelines. Calculations were based on a DerSimonian and Laird random effects model. Heterogeneity among trials was quantified with Higgins’s and Thompson’s I2, which can be interpreted as the percentage of variability due to heterogeneity between studies rather than sampling error. Publication bias was assessed by generating separate Funnel Plots for each of the two groups of studies. Findings are presented as point estimates and 95% confidence intervals, and when appropriate, weight of individual studies. All analyses were performed within RevMan version 5.1.

Results

Identification and selection of studies

Our initial electronic search yielded 654 citations, and an additional 27 were identified through hand-search of bibliographies and other sources. After an initial screen of titles, 100 abstracts were reviewed, and 22 of those were subsequently selected for full-text review. Six studies were excluded for lacking sufficient number of CCR elements, three studies excluded for sharing duplicative data with included studies, and one study for non-English language text. Finally, 12 total studies satisfied the predetermined inclusion criteria: three using Cardiocerebral Resuscitation and nine using AHA 2005 or ERC 2005 Guidelines, as shown in Figure 1.

Characteristics of included studies

The final sample included 12 studies, with approximately 19,634 subjects. Study characteristics and pertinent outcome data are shown in Table 2. All 12 articles that were included were prospective observational studies with data on survival pre- and post-
implementation of guidelines. Eight of the 12 studies were rated as high quality, and four were rated as medium quality. No randomized controlled trials were identified that met inclusion criteria.

Three studies, which included a total of 2,820 subjects, met the predetermined criteria for use of AHA 2000 (control) versus CCR (study) protocol.\textsuperscript{18-20} Nine studies, which included a total of 16,814 subjects, compared the use of AHA 2000/ERC 2000 (control) versus AHA 2005/ERC 2005 (study) protocols.\textsuperscript{21-29}

Eight of the studies were conducted in North America, and one each in Taiwan, Norway, New Zealand, and Denmark. Data on EMS control protocols (2000 Guidelines) were collected in the range of 2003 to 2006, except for Kellum (2008) which began collecting data in 2001. Data on EMS study protocols (CCR or AHA/ERC 2005 Guidelines) were collected in the range of 2004 to 2008. Of note, none of the studies using CCR, but five of studies using AHA 2005 Guidelines explicitly reported consistent use of therapeutic hypothermia during the study period.\textsuperscript{21 23 25 26 28}

The mean subject age across all studies was 64 years, and the mean gender distribution was 66.4% male. Two studies had significant differences in age between their control and study populations.\textsuperscript{22 25}

There was a wide range across studies in the proportion of OHCA receiving bystander CPR (8% to 58%) with a mean of 34.6%. The mean EMS response time was 6.2 minutes, with a range of 4.7 to 9.3 minutes. The mean proportion of OHCA patients with a presenting rhythm of ventricular fibrillation or ventricular tachycardia was 29.9%, with a range of 5.6% to 50%. Three studies reported statistically significant differences in the proportion of witnessed arrest, proportion of bystander-CPR, or response time between control and study populations.\textsuperscript{20 22 23}

Overall Outcomes

Survival to hospital discharge was identified as the primary or secondary outcome in all studies. Mean survival when using AHA/ERC 2000 Guidelines was 6.9% (range of 1.8% to 11.1%). Mean survival to discharge increased to 10.1% (6.5% - 19.4%) when using AHA/ERC 2005 Guidelines, and to 9.3% (5.4% to 18.3%) when Cardiocerebral Resuscitation was used. Overall mean survival across all studies and protocols was 9.7%.

AHA 2000 Guidelines as compared to CCR
All three of the studies using a CCR protocol showed significantly improved survival for CCR compared to use of AHA 2000 Guidelines. Pooled analysis of data from these studies (Figure 2) demonstrated a statistically significant survival benefit when using a CCR protocol, with a pooled odds ratio of 2.26 (95% CI: 1.64 – 3.12). Heterogeneity among the studies was not significant (I² = 0.0%, p=0.61).

Subgroup analysis of the patients with a presenting rhythm of witnessed ventricular fibrillation/ventricular tachycardia showed a significant association with survival for the CCR protocol as compared to the AHA 2000 Guidelines. Pooled odds ratio of survival to hospital discharge for this subgroup was 2.98 (95% CI: 1.92 – 4.62) (Figure 2). The funnel plot of these three studies was not suggestive of publication bias (Supplemental Figure 1).

**AHA/ERC 2000 Guidelines as compared to AHA/ERC 2005 Guidelines**

Eight of the nine studies using AHA/ERC 2005 Guidelines demonstrated improved survival to hospital discharge for use of AHA/ERC 2005 compared to AHA/ERC 2000 guidelines, a result that was statistically significant in five out of nine studies (Figure 3). Although the overall trend was towards a survival benefit for AHA/ERC 2005 Guidelines, heterogeneity tests revealed significant heterogeneity among these nine studies (I² = 72%, p=0.0004), so a pooled odds ratio for survival was not calculated.30

Subgroup analysis of the patients with a presenting rhythm of witnessed ventricular fibrillation/ventricular tachycardia showed a trend toward improved survival for the AHA/ERC 2005 Guidelines as compared to the AHA/ERC 2000 Guidelines. However, there was significant heterogeneity between studies so a pooled odds ratio was not calculated.30 The funnel plot of these nine studies was not suggestive of publication bias (Supplemental Figure 2).

**Discussion**

**Main Findings**

In our systematic review of 12 studies and 19,634 subjects, we found a consistent and significant survival benefit from out-of-hospital cardiac arrest when EMS transitioned to use of updated resuscitation protocols. Our meta-analysis findings suggest that, compared to AHA 2000 Guidelines, use of CCR has a significant association with increased survival for all OHCA patients. In our subgroup analysis of patients with a presenting rhythm of VF/VT, use of a CCR protocol was associated with nearly a 3-fold increase in survival. This association was not as
clear in the comparison of the AHA/ERC 2000 to AHA/ERC 2005 Guidelines, as there was a trend toward improved survival, but a pooled odds ratio could not be calculated secondary to heterogeneity between studies. Although a pooled estimate of effect was not possible for this set of studies, the 2005 updates to resuscitation guidelines appear to have led to a demonstrable effect on OHCA survival.

It appears that both the CCR protocols and AHA/ERC 2005 Guidelines are associated with overall increases in survival from OHCA. After years of unchanged survival rates, this is a promising new finding. Furthermore, the association with improved survival is seen most clearly in the studies using a CCR protocol. Based on animal models and human studies, it is likely that multiple elements of the AHA/ERC 2005 Guidelines and CCR protocols have contributed to this progress. Both the AHA/ERC 2005 Guidelines and CCR emphasize the need to maintain coronary and cerebral perfusion pressure by minimizing interruptions in chest compressions, although CCR eliminates any stoppage for ventilations. The benefits of this emphasis on optimal chest compression depth and continuous rate of chest compressions have been shown in multiple animal studies. In addition, both protocols emphasize 150-200 compressions immediately prior and immediately after defibrillation attempts, in recognition of the evidence that a perfused heart is much more likely to convert to a pulsatile rhythm after shock. These changes endorsed by the AHA and ERC 2005 Guidelines have likely contributed heavily to the demonstrated progress in OHCA survival.

However, the most significant difference between AHA/ERC 2005 Guidelines and CCR protocols is the decision to delay intubation in favor of passive ventilation. An existing body of studies has shown that intubations can 1) cause significant delays and/or interruptions in chest compressions, and 2) lead to excessive positive pressure ventilation which can reduce venous return, reduce cerebral and coronary perfusion pressures, and consequently reduce likelihood of survival.

The benefit of passive insufflation was recently shown in a sub-analysis of the “minimally interrupted cardiac resuscitation” protocol used in Arizona and included in this meta-analysis through Bobrow et al. (2008). Due to reluctance of EMS teams to forgo active ventilation, this protocol allowed airway management through either passive insufflation or bag-valve-mask ventilation, at the discretion of the paramedics. For the subset of patients most likely to survive (witnessed VF/VT), neurologically intact survival was significantly higher among patients who received passive insufflation only as compared to bag-valve mask (38.2% compared to 25.8%).
Another study, published in 2011, showed an association with increased survival when a non-standard resuscitation protocol was implemented in Sussex County, United Kingdom. Delayed ventilation was a key feature in this protocol; patients with witnessed OHCA and initial VF/VT were not given any active ventilations until after three cycles of 100 compressions plus shock. Using this strategy, survival in these patients increased from a historical baseline of 13% to approximately 30%.

The newest ERC and AHA Guidelines were recently released in late-2010. The ERC Guidelines have removed the recommendation for a specified period of CPR prior to first defibrillation, while the AHA Guidelines have a strong emphasis on C-A-B: compressions, airway and then breathing. The shift to focusing on providing quality chest compression at a rate of at least 100 per minute is a change from the AHA 2000 and 2005 guidelines in which the airway and breathing were first addressed. Although this is similar to the approach to CCR, there are still significant differences, the most significant being that CCR encourages compressions without ventilations. Future research will need to be conducted to directly compare survival between use of the updated AHA and ERC 2010 Guidelines and use of CCR.

Limitations:

This systematic review yielded a total of 12 studies reporting results on CCR and AHA/ERC 2005 Guidelines as compared to AHA/ERC 2000 Guidelines. This relatively small sample limits the generalizability of our results in several ways. Only three studies reported results from the use of CCR protocols, which limited the meta-analysis to include only 2820 total subjects. Additionally, some of the included studies reported few total patients surviving to hospital discharge, and thus were not as heavily weighted in the meta-analysis. However, even with a small number of studies and total subjects, this meta-analysis was sufficiently powered to demonstrate a significant survival benefit. Finally, although our Funnel Plots did not suggest a significant publication bias, it is possible that unpublished, negative studies were underrepresented in our review. Future research from multiple research centers across the U.S. and internationally could potentially strengthen the results demonstrated here.

All of the included studies report data from observational studies; no randomized-controlled trials were found that met inclusion criteria, and thus this review was unable to locate studies of the highest scientific quality. Indeed, randomization of OHCA patients to different EMS protocols is impractical and ethically problematic. All of the observational studies included in
this review were found to be of high or medium methodological quality based on the NOS, but
due to inherent weaknesses in observational studies there exists the potential for confounding
and bias within these studies. The combination of multiple observational studies into a meta-
analysis has the potential limitation of masking confounders that exist within the individual
studies. These confounders may include a number of unrecognized variables of cardiac
resuscitation, as well as possible changes made to the emergency health care systems between
the “control” and “study” protocols, such as community education or improved quality of chest
compressions by EMS. Additionally, it is possible that the survival improvement demonstrated
here with newer protocols is confounded by temporal changes in the communities studied.
Changes in community demographics or disease burden that occurred between and within the
periods of data collection could have contributed to the observed changes in survival. The
overall similarity in demographics and characteristics of the “control” and “study” subjects (as
reported in the individual studies) makes it unlikely that this potential confounder has had a
significant influence on our overall results. However, the existence of other, unrecognized
confounders of the individual studies remains an important limitation to our meta-analysis.

The introduction of therapeutic hypothermia represents another important possible
limitation to the interpretation of these results. The use of post-arrest hypothermia was not
consistent between “control” and “study” protocols of individual studies. Four of the nine studies
using AHA 2005 Guidelines reported significantly increased use of therapeutic hypothermia
during the “study” protocol period (two other studies did not mention change in hypothermia
use). Given the strong evidence for the benefit of therapeutic hypothermia\textsuperscript{43-44}, it is thus likely
that the use of hypothermia contributed to the overall trend towards improved survival; our
analysis is limited in its ability to calculate the magnitude of that contribution. However,
therapeutic hypothermia was not used on any of the patients included in the three CCR studies.
Thus, it is extremely unlikely that hypothermia alone could be an alternative explanation for the
increase in survival demonstrated by use of the CCR protocols.

The heterogeneity of the nine studies using AHA 2005 or ERC 2005 guidelines precluded
pooling of their data and a summary estimate of effect. These studies were also heterogeneous
in the specifics of the resuscitation protocols used, many employing minor deviations from the
AHA or ERC guidelines. For example, both the “control” and “study” protocols of Sayre et al.
(2009) utilized 2 minutes of CPR prior to first defibrillation attempt, and Steinmetz et al. (2009)
utilized a mechanical compression device. Additionally, there exist minor but important
differences between the AHA and ERC resuscitation guidelines. While these variations might have influenced the results of the individual studies, the random-effects model used for our pooled data analysis accounted for some of this variability. Still these variations serve to highlight the difficulty of standardizing resuscitation protocols and comparing EMS systems.

Although delayed intubation is one of the pillars of Cardiocerebral Resuscitation, the three studies included in the “AHA 2000 as compared to CCR” group all utilized different protocols for airway management during the “study” protocol time period. The Kansas City Missouri (KCMO) protocol used in Garza et al. (2009) used a 50:2 compression to ventilation ratio. Kellum et al. (2010) delayed intubation for patients with shockable rhythms only. Most significantly, Bobrow et al. (2008) allowed bag-valve-mask ventilation at the paramedics’ discretion. The differences in the airway management strategies of these three studies makes it more difficult to assess which aspects of the CCR protocol contributed most to increased survival, and limits the generalizability of our results.

Conclusions:

The results of this systematic review and meta-analysis demonstrate an association with survival from OHCA when CCR protocols or AHA/ERC 2005 Guidelines are compared to AHA/ERC 2000 Guidelines. Although no randomized trials have yet been reported, multiple high quality observational studies have demonstrated an association with increased survival post-AHA/ERC 2005 guideline or CCR implementation. Additionally, in the pooled subgroup of witnessed VF/VT patients, there was a three-fold increase in OHCA survival after a CCR protocol was implemented. The focus of the updated AHA 2010 and ERC 2010 Guidelines shifts emphasis toward providing uninterrupted, quality chest compressions. However these changes still do not incorporate key elements of the CCR protocol that this study indicates are associated with improved OHCA survival, such as passive insufflation and minimal interruptions of chest compressions. Our study suggests that CCR appears to be a promising resuscitation protocol for EMS providers in increasing survival from OHCA. Future research will need to be conducted to directly compare AHA/ERC 2010 Guidelines with the CCR approach.

Authors’ contributions: MS, CS conceptualized and designed this systematic review and meta-analysis. MS, CS were substantially involved in data acquisition (literature search, study selection, and data abstraction). MS, CS performed the analyses and were substantially involved in data interpretation. MS, GE, CS provided data used for the analysis and relevantly contributed to the interpretation and intellectual content of the manuscript. MS, CS drafted the
manuscript. All authors revised the manuscript critically for important intellectual content. All authors approved the final version.

Funding: This project received no specific funding

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Ethical approval: not required

Data sharing: available from authors upon request

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**Box: Inclusion criteria for eligible studies**

**Study Design:** Randomized controlled trials and observational studies

**Population:** Out-of-Hospital Cardiac Arrest patients, >17 years of age.

**EMS Control Protocol:** AHA 2000 Guidelines or ERC 2000 Guidelines for Cardiopulmonary Resuscitation

**EMS Study Protocol:** AHA 2005 Guidelines or ERC 2005 Guidelines for Cardiopulmonary Resuscitation, or Cardiocerebral Resuscitation

**Outcomes:** Rate of bystander CPR, EMS response time, Proportion of initial VF/VT, and Survival to hospital discharge

**Quality:** High or Medium quality, as categorized using the Newcastle Ottawa Scale (NOS) for cohort studies.
Table 1: AHA vs ERC vs CCR Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Compressions</th>
<th>Ventilation</th>
<th>Defibrillation</th>
</tr>
</thead>
</table>
| **AHA 2000 CPR** | 15:2 ratio   | **Tracheal Intubation** 10-12 breaths/min | Pre: ---  
  * Triple Shock  
  * Pulse Check  
  Post: 1 min CPR |
| **ERC 2000 CPR** | 15:2 ratio   | **Tracheal Intubation** ~12 breaths/min | Pre: ---  
  * Triple Shock  
  Post: 1 min CPR  
  * Pulse Check * |
| **AHA 2005 CPR** | 30:2 ratio   | **Tracheal Intubation** 8-10 breaths/min | Pre: Optional 5 cyc  
  * Single Shock  
  Post: 5 cycles  
  * Pulse Check * |
| **ERC 2005 CPR** | 30:2 ratio   | **Tracheal Intubation** 8-10 breaths/min | Pre: 2 min CPR  
  * Single Shock  
  Post: 2 min CPR  
  * Pulse Check * |
| **Cardiocerebral Resuscitation (2003)** | Continuous 100/min | **Passive Only; Delayed Intubation** | Pre: 200 compress  
  * Single Shock  
  Post: 200 compress  
  * Pulse Check * |
Figure 1: Flow chart depicting the outline of study selection process

654 potentially relevant citations identified through database searching

27 additional citations identified through hand-search of bibliographies and other sources

681 citations screened by title & abstract for potential inclusion

Excluded, n=581
n=581: Reviews, opinions, clear irrelevance, duplicates

100 potential citations for secondary review

Excluded, n=78
n=37: Comment, reviews, Utstein reports
n=20: Bystander CPR/dispatcher CPR
n=10: Only partial elements of CCR
n=4: Focus on EMS ACLS
n=4: Meeting abstracts only
n=3: Mechanical CPR devices

22 studies comparing AHA 2000, Guidelines to AHA 2005 Guidelines or CCR protocol

Excluded, n=10
n=6: Incomplete criteria for CCR
n=3: Duplicative data of included studies
n=1: Non-English language

Stage 1: Review of title or abstract

Stage 2: Review of abstract

Stage 3: Full-text review

Included in Review

3 studies meeting complete CCR criteria

9 studies of AHA guideline changes
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Quality</th>
<th>Study Protocol</th>
<th>Control vs. Study Protocol</th>
<th>Bystander CPR (%)</th>
<th>Response Time (min)</th>
<th>Initial VF/VT (%)</th>
<th>Total Arrests (n)</th>
<th>Survival to Discharge (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bobrow (2008)</td>
<td>Arizona</td>
<td>High</td>
<td>AHA 2000</td>
<td>AHA 2000</td>
<td>34</td>
<td>5.6</td>
<td>31.7</td>
<td>218</td>
<td>4 (1.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Micro (MICR)</td>
<td>39</td>
<td>5.2</td>
<td>29.9</td>
<td>668</td>
<td>36</td>
<td>36 (5.4%)</td>
</tr>
<tr>
<td>Garza (2009)</td>
<td>Missouri</td>
<td>High</td>
<td>AHA 2000</td>
<td>AHA 2000</td>
<td>38</td>
<td>5.4</td>
<td>31.4</td>
<td>1097</td>
<td>64 (5.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>KCMO Protocol</td>
<td>KCMO Protocol</td>
<td>47</td>
<td>5.3</td>
<td>33.3</td>
<td>339</td>
<td>37 (10.9%)</td>
</tr>
<tr>
<td>Kellum (2008)</td>
<td>Wisconsin</td>
<td>High</td>
<td>AHA 2000</td>
<td>AHA 2000</td>
<td>45</td>
<td>7.4</td>
<td>42.5</td>
<td>268</td>
<td>21 (7.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CCR</td>
<td>CCR</td>
<td>45</td>
<td>8.6</td>
<td>47.4</td>
<td>230</td>
<td>42 (18.3%)</td>
</tr>
<tr>
<td>Aufderheide (2010)</td>
<td>MN, TX, NE, FL, NC</td>
<td>High</td>
<td>AHA 2000</td>
<td>AHA 2000</td>
<td>38</td>
<td>5.6</td>
<td>25.3</td>
<td>1641</td>
<td>166 (10.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AHA 2005</td>
<td>AHA 2005</td>
<td>40</td>
<td>5.6</td>
<td>23.9</td>
<td>1605</td>
<td>211 (13.1%)</td>
</tr>
<tr>
<td>Bigham (2011)</td>
<td>Canada &amp;</td>
<td>Medium</td>
<td>AHA 2000</td>
<td>AHA 2000</td>
<td>29</td>
<td>5.8</td>
<td>23.1</td>
<td>5054</td>
<td>294 (5.8%)</td>
</tr>
</tbody>
</table>
Minimally Interrupted Cardiac Resuscitation (MICR) allowed either passive insufflation or bag-valve-mask ventilation at paramedic discretion.

Kansas City, Missouri (KCMO) Protocol included a 50:2 compression to ventilation ratio.

These values represent the sub-population of witnessed VF/VT.

Values are reported from “Phase 3” of the step-wise introduction of AHA 2005 guidelines.

These protocols represent the “Pre” and “Post” states of a community intervention.

Both protocols used 2 minutes of CPR prior to the first defibrillation.

This protocol used an automated compression device (AutoPulse™).

Quality categorized as High, Medium, or Low using the Newcastle Ottawa Scale, similar to other recent meta-analyses.

---

**Figure 2: Forest Plot of Pooled Odds Ratios: CCR vs. AHA 2000 Studies**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CCR Protocol Events</th>
<th>Total</th>
<th>AHA 2000 Guidelines Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bobrow (2008)</td>
<td>36</td>
<td>668</td>
<td>4</td>
<td>218</td>
<td>9.5%</td>
<td>3.05 [1.07, 8.6]</td>
<td></td>
</tr>
<tr>
<td>Garza (2009)</td>
<td>37</td>
<td>339</td>
<td>64</td>
<td>1097</td>
<td>57.3%</td>
<td>1.98 [1.29, 3.02]</td>
<td></td>
</tr>
<tr>
<td>Kellom (2008)</td>
<td>42</td>
<td>230</td>
<td>21</td>
<td>258</td>
<td>33.3%</td>
<td>2.63 [1.51, 4.59]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1237</td>
<td>1583</td>
<td>100.0%</td>
<td>2.26</td>
<td>1.64, 3.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>115</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 2 (P = 0.61); I² = 0%

Test for overall effect: Z = 4.99 (P < 0.0001)

---

**Figure 3: Forest Plot of Odds Ratios for Witnessed VF/VT Survival: CCR vs. AHA/ERC 2000 Studies**
Figure 4: Forest Plot of Odds Ratios: AHA/ERC 2005 vs. AHA/ERC 2000 Studies

References:


Supplemental Figure 1: Funnel Plot of CCR vs. AHA 2000 Studies

Supplemental Figure 2: Funnel Plot of AHA/ERC 2005 vs. AHA/ERC 2000 Studies
Use of Cardiocerebral Resuscitation or AHA 2005 Guidelines Improves Survival from Out-of-Hospital Cardiac Arrest: Systematic Review & Meta Analysis

Marcus Salmen, B.S.¹, Gordon Ewy M.D.², Comilla Sasson, M.D., M.S.³

MOOSE Checklist

<table>
<thead>
<tr>
<th>Table. A Proposed Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting of background should include</td>
</tr>
<tr>
<td>✓ Problem definition</td>
</tr>
<tr>
<td>✓ Hypothesis statement</td>
</tr>
<tr>
<td>✓ Description of study outcome(s)</td>
</tr>
<tr>
<td>✓ Type of exposure or intervention used</td>
</tr>
<tr>
<td>✓ Type of study designs used</td>
</tr>
<tr>
<td>✓ Study population</td>
</tr>
<tr>
<td>Reporting of search strategy should include</td>
</tr>
<tr>
<td>✓ Qualifications of searchers (e.g., librarians and investigators)</td>
</tr>
<tr>
<td>✓ Search strategy, including time period included in the synthesis and keywords</td>
</tr>
<tr>
<td>✓ Effort to include all available studies, including contact with authors</td>
</tr>
<tr>
<td>✓ Databases and registries searched</td>
</tr>
<tr>
<td>✓ Search software used, name and version, including special features used (e.g., explosion)</td>
</tr>
<tr>
<td>✓ Use of hand searching (e.g., reference lists of obtained articles)</td>
</tr>
<tr>
<td>✓ List of citations located and those excluded, including justification</td>
</tr>
<tr>
<td>✓ Method of addressing articles published in languages other than English</td>
</tr>
<tr>
<td>✓ Method of handling abstracts and unpublished studies</td>
</tr>
<tr>
<td>✓ Description of any contact with authors</td>
</tr>
<tr>
<td>Reporting of methods should include</td>
</tr>
<tr>
<td>✓ Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested</td>
</tr>
<tr>
<td>✓ Rationale for the selection and coding of data (e.g., sound clinical principles or convenience)</td>
</tr>
<tr>
<td>✓ Documentation of how data were classified and coded (e.g., multiple raters, blinding, and interrater reliability)</td>
</tr>
<tr>
<td>✓ Assessment of confounding (e.g., comparability of cases and controls in studies where appropriate)</td>
</tr>
<tr>
<td>✓ Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results</td>
</tr>
<tr>
<td>✓ Assessment of heterogeneity</td>
</tr>
<tr>
<td>✓ Description of statistical methods (e.g., complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated</td>
</tr>
<tr>
<td>✓ Provision of appropriate tables and graphics</td>
</tr>
<tr>
<td>Reporting of results should include</td>
</tr>
<tr>
<td>✓ Graphic summarizing individual study estimates and overall estimate</td>
</tr>
<tr>
<td>✓ Table giving descriptive information for each study included</td>
</tr>
<tr>
<td>✓ Results of sensitivity testing (e.g., subgroup analysis)</td>
</tr>
<tr>
<td>✓ Indication of statistical uncertainty of findings</td>
</tr>
<tr>
<td>Reporting of discussion should include</td>
</tr>
<tr>
<td>✓ Quantitative assessment of bias (e.g., publication bias)</td>
</tr>
<tr>
<td>✓ Justification for exclusion (e.g., exclusion of non-English-language citations)</td>
</tr>
<tr>
<td>✓ Assessment of quality of included studies</td>
</tr>
<tr>
<td>Reporting of conclusions should include</td>
</tr>
<tr>
<td>✓ Consideration of alternative explanations for observed results</td>
</tr>
<tr>
<td>✓ Generalization of the conclusions (i.e., appropriate for the data presented and within the domain of the literature review)</td>
</tr>
<tr>
<td>✓ Guidelines for future research</td>
</tr>
<tr>
<td>✓ Disclosure of funding source</td>
</tr>
</tbody>
</table>

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Correction


Figure 1 in this article was mislabelled and should have been: "**Figure 1** AHA versus ERC versus cardiocerebral resuscitation characteristics." Figure 2 should have been: "**Figure 2** Flow chart depicting the outline of study selection process." Figure 3 should have been: "**Figure 3** Forest plot of pooled ORs: cardiocerebral resuscitation versus AHA 2000 studies.

In addition, the second sentence of the first full paragraph of page 5 contains an error. It is stated "Pooled OR of survival to hospital discharge for this subgroup was 2.98 (95% CI 1.92 to 4.62) (figure 3))." In fact, this needs to be “(figure 4)”, and not the figure 4 that is currently included in the manuscript. The correct version of figure 4 is below. The correct label should be "**Figure 4** Forest plot of ORs for witnessed ventricular fibrillation/ventricular tachycardia survival: cardiocerebral resuscitation versus AHA/ERC 2000 studies." The second paragraph on the fifth page, left column, should then read: "Eight of the nine studies using AHA/ERC 2005 Guidelines demonstrated improved survival to hospital discharge for use of AHA/ERC 2005 compared to AHA/ERC 2000 Guidelines, a result that was statistically significant in five out of nine studies (figure 5)."

We apologise for these errors.