Identifying Important Gaps in Randomized Controlled Trials of Adult Cardiac Arrest Treatments

A Systematic Review of the Published Literature

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Background—Cardiac arrest is a major public health concern worldwide. The extent and types of randomized controlled trials (RCT)—our most reliable source of clinical evidence—conducted in these high-risk patients over recent years are largely unknown.

Methods and Results—We performed a systematic review, identifying all RCTs published in PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Library from 1995 to 2014 that focused on the acute treatment of nontraumatic cardiac arrest in adults. We then extracted data on the setting of study populations, types and timing of interventions studied, risk of bias, outcomes reported, and how these factors have changed over time. Over this 20-year period, 92 RCTs were published containing 64 309 patients (median, 225.5 per trial). Of these, 81 RCTs (88.0%) involved out-of-hospital cardiac arrest, whereas 4 (4.3%) involved in-hospital cardiac arrest and 7 (7.6%) included both. Eighteen RCTs (19.6%) were performed in the United States, 68 (73.9%) were performed outside the United States, and 6 (6.5%) were performed in both settings. Thirty-eight RCTs (41.3%) evaluated drug therapy, 39 (42.4%) evaluated device therapy, and 15 (16.3%) evaluated protocol improvements. Seventy-four RCTs (80.4%) examined interventions during the cardiac arrest, 15 (16.3%) examined post cardiac arrest treatment, and 3 (3.3%) studied both. Overall, reporting of the risk of bias was limited. The most common outcome reported was return of spontaneous circulation: 86 (93.5%) with only 22 (23.9%) reporting survival beyond 6 months. Fifty-three RCTs (57.6%) reported global ordinal outcomes, whereas 15 (16.3%) reported quality-of-life. RCTs in the past 5 years were more likely to be focused on protocol improvements and postcardiac arrest care.

Conclusions—Important gaps in RCTs of cardiac arrest treatments exist, especially those examining in-hospital cardiac arrest, protocol improvement, postcardiac arrest care, and long-term or quality-of-life outcomes. **(*Circ Cardiovasc Qual Outcomes*. 2016;9:749-756. DOI: 10.1161/CIRCOUTCOMES.116.002916.)**

Key Words: cardiopulmonary resuscitation ■ heart arrest ■ health services research ■ randomized controlled trial ■ resuscitation

Cardiac arrest is a serious public health concern worldwide.[1,2] Approximately 347 000 out-of-hospital cardiac arrest (OHCA) and 209 000 in-hospital cardiac arrest (IHCA) occur in adults each year in the United States,[1] with millions more occurring across the rest of North America, Europe, and Asia.[3] Although survival has increased significantly in the past decade,[4,5] it remains unacceptably low,[6,7] despite considerable attention devoted toward enhancing emergency response systems, high-quality and bystander cardiopulmonary resuscitation, immediate defibrillation, and postarrest care therapies, such as therapeutic hypothermia.[8,9] This lack of improvement is striking in contrast to other cardiovascular diseases, such as acute myocardial infarction, which have seen dramatic improvements in early and late mortality.[10]

A potential reason for limited progress in cardiac arrest treatments may result from a lack of randomized controlled trials (RCTs)—traditionally, the most reliable source of clinical evidence for medical treatments.[11] Indeed, a recent expert opinion piece[12] and Institute of Medicine report[2] have cited minimal investment in research and infrastructure for RCTs to study

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WHAT IS KNOWN

- Approximately 347 000 OHCA and 209 000 IHCA occur in adults each year in the United States, with millions more occurring across the rest of North America, Europe, and Asia.
- Although survival has increased significantly in the past decade, it remains unacceptably low.

WHAT THE STUDY ADDS

- In this systematic review, we found 92 RCTs with 64 309 patients published between 1995 and 2014.
- There is an overall lack of RCTs in adult cardiac arrest relative to its disease burden.
- Several important gaps were identified in RCTs, including the infrequent focus on in-hospital cardiac arrest, protocol improvements, postcardiac arrest care, and long-term or quality-of-life outcomes.

cardiac arrest treatments relative to its high disease burden in the general population. Yet, despite this potential mismatch between the published science and the public health burden of cardiac arrest, there is little objective information that exists to guide where exactly contemporary RCTs may be most deficient or where specific opportunities for advancement with future trials may be greatest. In particular, the focus, design, and quality of RCTs that target treatments in cardiac arrest are largely unknown but could vary significantly, as the condition covers broad populations and heterogeneous therapies.

Accordingly, we performed a systematic review of RCTs in cardiac arrest treatment performed over the past 20 years, focusing on the key aspects of their design, including the setting of the study populations (OHCA and IHCA), the types of interventions studied (ie, drug, device, or protocol improvement), timing (ie, during the cardiac arrest or after the return of spontaneous circulation [ROSC]), risk of bias, and outcomes reported (ie, process measure, ROSC, survival to discharge, long-term survival, global ordinal outcomes, and quality-of-life). Our findings have implications for both the current management of cardiac arrest and the prioritization of future work.

Methods

Data Sources, Study Identification, and Selection

We performed a systematic review using guidelines from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[13] A comprehensive, computerized literature search of the following electronic databases was conducted: PubMed, EMBASE, Scopus, Web of Science, and the Cochrane Library. We identified relevant English language studies published from January 1, 1995 to December 31, 2014 utilizing keywords and controlled vocabulary terms (MeSH and EMTREE) related to cardiac arrest. We included medical subject headings (MeSH) terms heart arrest, cardiac arrest, and cardiopulmonary resuscitation, with the PubMed Clinical Queries Narrow Therapy filter limiting the search to primarily randomized or other controlled clinical trials. Full details of the replicable search strategies for each of the databases and a PRISMA checklist are available in Appendices III and IV in the Data Supplement, respectively. Abstracts from conferences, proceedings or clinical trial registries were not included, as we were interested in RCTs that were ultimately published in peer-reviewed literature. We also manually reviewed bibliographies of included RCTs and recent Cochrane reviews to identify references we may have missed during our primary search.

Titles and abstracts from all initially retrieved articles were independently reviewed by 3 investigators (S.S.S., D.S., and J.J.L.) for potential inclusion in the study. We included a study if it involved adult human subjects with nontraumatic cardiac arrest where treatments were applied either during the arrest or immediately post cardiac arrest (within 24 hours of ROSC). We excluded RCTs of public health interventions; primary or secondary prevention of cardiac arrest in high-risk patients (eg, implantable cardioverter defibrillators); animal studies; studies that exclusively included neonatal or pediatric patients; simulation studies; and studies of provoked cardioplegic arrest (eg, cardiac surgery). Trials were also excluded if the primary population included patients with conditions in addition to cardiac arrest (eg, sepsis, cardiogenic shock, or ST-elevation–elevation myocardial infarction). Finally, our primary analysis eliminated RCTs that primarily piloted the feasibility of new, highly exploratory treatments by restricting our cohort to those with at least 50 patients. We did extract several data elements from these smaller reports and provide them in the Appendix in the Data Supplement. If multiple reports shared the same cohort (ie, interim analyses, prespecified substudies, or studies published in multiple journals), we only included the report with the largest study population in our primary analysis (although data from the additional reports were included in our evaluation of outcome assessments when relevant).

After retrieving full articles of potentially relevant trials, 2 reviewers (S.S.S. and D.S.) independently assessed each study's eligibility on the basis of these inclusion and exclusion criteria. Any discrepant opinions were resolved through consensus or consultation with a third investigator (B.K.N.).

Data Extraction and Risk of Bias Assessment

Information from each RCT was extracted independently by at least 2 of 3 reviewers (S.S.S., D.S., and J.J.L.) using a standardized form. The following variables were collected: author, title, journal and year of publication, location of arrest (OHCAs, IHCAs, or both), initial cardiac arrest rhythm (pulseless ventricular tachycardia/ventricular fibrillation, asystole/pulseless electric activity, or both), size (number randomized to primary analysis) and patient characteristics of the study population (age, sex, witnessed arrest, and provision of bystander CPR), type of intervention (drug, device and protocol improvement), and the timing of intervention (during cardiac arrest [ie, pre-ROSC] or immediately post cardiac arrest [ie, post-ROSC]). We extracted the mean (and if not available, median) age of both intervention and control/placebo arms of each RCT. For those trials with multiple intervention arms or multiple sites represented, we calculated a weighted average based on reported data. For example, if a given study had an intervention A with sample size 100 with an average age of 60 years, and intervention B with sample size 200 with an average age of 65 years, the weighted mean would be: $(60\times100)+(65\times200)/300=63.3$. For the purposes of this systematic review, our interest was at the level of RCTs and not patients. Thus, we did not account for differential study-specific sample sizes. We also extracted study design features such as single versus multicenter trial, geographic location (United States, non-United States, and both), and source of funding (government, industry, hospital/institutional, none, or not reported). Missing data were extracted as unavailable.

By necessity, we relied on each RCT's definitions for several key variables, which were consistent across studies for most but not all variables. For example, bystander CPR was typically defined as any attempt at CPR initiated by a person other than the Emergency Medical Services or first responder team regardless of whether the event was witnessed. Our assessment of whether an RCT studied a protocol improvement was defined by us as an intervention that examined a change in timing or approach for implementing a treatment (eg, prehospital therapeutic hypothermia versus routine care with hospital-initiated therapeutic hypothermia) and not if the treatment was given or not.

We also extracted data on outcome assessments in each RCT and how these outcomes were reported in the article (positive if the primary null hypothesis defined by the authors was rejected, negative if not). For consistency, we categorized outcomes into the following groups: process measures, outcome measures, ROSC, survival to hospital discharge, 30-day to 6-month survival, long-term survival (defined as greater than 6 months), neurological outcomes, global ordinal outcomes, or quality-of-life. Although no single measurement has been validated to completely characterize neurological status after acute cardiac arrest, neurological assessments included the National Institutes of Health Stroke Scale (NIHSS) and Full Outcome of Responsiveness (FOUR) score for comatose patients. Similarly, global ordinal outcomes, adopted from the taxonomy developed by the 2011 AHA Consensus Statement on "Primary Outcomes for Resuscitation Science Studies,"[14] included the following functional outcome measures: cerebral performance category, overall performance category, Glasgow Coma Scale (GCS), Glasgow-Pittsburgh Coma Scale (GPCS), Glasgow Outcome Scale (GOS), modified Rankin Scale (mRS), or other functional outcome measures. Cognitive measures such as the mini-mental status examination were grouped under other functional outcome measure. Quality-of-life measures included any assessments, such as those evaluating physical and psychological perceived health status, functional status (ie, activities of daily living, occupational status, and discharge destination), or other relevant measures.

Finally, 2 reviewers (S.S.S. and D.S.) assessed the risk of bias using the Cochrane assessment tool,[15] modified to focus on the following domains most relevant to RCTs in cardiac arrest: sequence generation, allocation concealment, blinding of primary personnel, blinding of primary outcome assessors, and blinding of global ordinal/quality-of-life outcome assessors. We did not consider blinding of subjects to be a key element of study design, as subjects experiencing cardiac arrest are unaware of the intervention(s). Furthermore, blinding of personnel and providers is not feasible in many cardiac arrest trials because of the type(s) of interventions studied (ie, active compression–decompression devices, timing of chest compressions, and defibrillation during CPR). Nevertheless, these studies were deemed to be high risk for this domain. Any disagreements in assessment between reviewers were resolved through discussions or consultation between investigators (S.S.S., D.S., and B.K.N.).

Statistical Analysis

Characteristics of RCTs were reported in absolute values and percentages. Because we were particularly interested in study characteristics of recent clinical trials, we compared the prevalence of these in the past 5 years of the study period (2010–2014) relative to earlier periods (1995–2009) using simple logistic regression models with the past 5 years of the study period as the dependent variable. The characteristics we independently evaluated included: number of subjects, location of arrest (OHCA and IHCA), single versus multicenter trial, geographic location, source of funding, type and timing of intervention, and outcomes assessment. We considered a P value of <0.05 as indicating statistical significance. All analyses were performed using Stata 14.0 (Stata Corporation, College Station, TX).

Results

Study Characteristics

Our initial search returned 5394 citations published between January 1, 1995 and December 31, 2014. We identified 248 studies for full-text review, with a total of 114 RCTs identified. Twenty-two of these studies enrolled less than 50 patients because they were largely piloting the feasibility of highly exploratory treatments and were eliminated. Thus, 92 RCTs of cardiac arrest containing 64 309 subjects met final eligibility criteria for inclusion (Appendix I in the Data Supplement). The final selection of studies for inclusion is displayed in Figure 1. The mean and median study population was 699 (SD, 1482) and 225.5 (IQR, 119–703.75), respectively, with mean age of 65.6 years (SD, 3.2) and 69.7% (SD, 8.6%) men. Appendix Table I in the Data Supplement lists the 92 RCTs individually by their journal publication and year, along with select study characteristics.

A total of 81 RCTs with 60 447 subjects involved OHCA exclusively, whereas 4 RCTs with 724 subjects involved IHCA exclusively and 7 RCTs with 3138 subjects involved both locations of arrest. Eighteen trials (19.6%) containing 7687 patients were performed in the United States, 68 (73.9%)

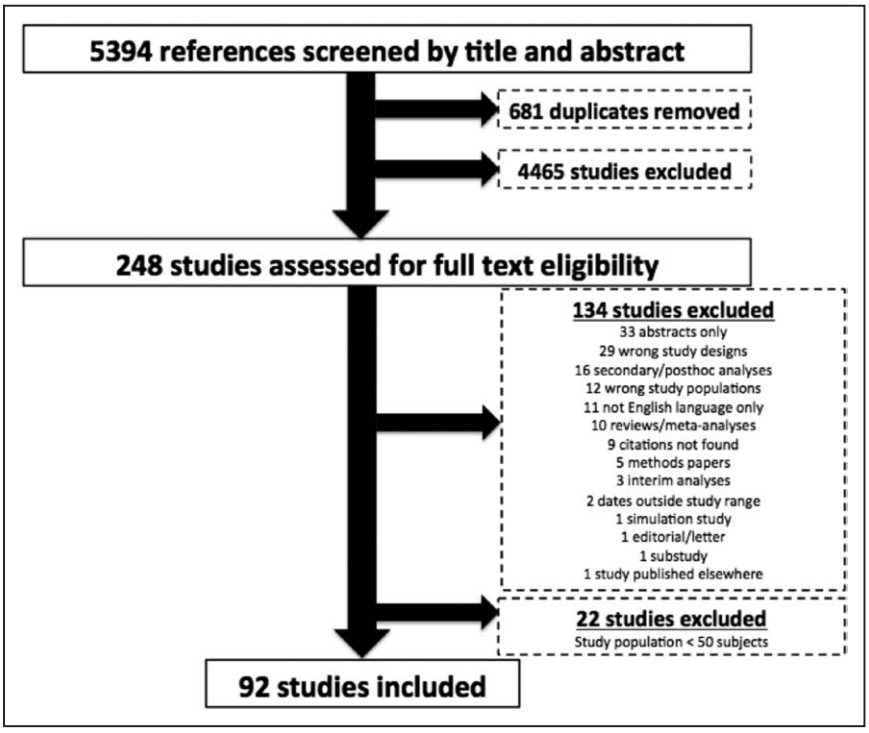

Figure. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the selection of randomized controlled trials.

comprised 30 400 subjects were performed outside the United Subjects, and 6 (6.5%) containing 26 222 subjects were performed in both settings. Of note, 5 of the 6 studies performed in both the locations (ie, US and abroad) were performed within the past 5 years. Table 1 provides summary statistics of several study characteristics for the 92 RCTs, stratified by the location of arrest as OHCA, IHCA, or both. More studies were performed in the past 5-year period between 2010 and 2014, when compared with earlier years. Fifty-two (56.5%) RCTs were industry sponsored, whereas 16 (17.4%) were government funded. Thirty-eight (41.3%) RCTs studied drugs, an additional 39 (42.4%) studied devices, and 15 (16.3%) studied protocol improvements. None of the 4 IHCA studies examined device or protocol interventions but focused entirely on evaluating drugs. Seventy-four (80.4%) RCTs examined interventions during the cardiac arrest, 15 (16.3%) examined post-cardiac arrest care, and 3 (3.3%) studied both.

Risk of Bias and Outcomes Assessed

A review of risk of bias of the RCTs revealed significant heterogeneity with an overall limited reporting of specific criteria (Table 2). Specifically, risk of bias was often difficult to assess because of the frequent absence of detailed reporting, often resulting in the attribution of unclear risk of bias. This was most frequently observed when reporting sequence generation (59.8%), allocation concealment (47.8%), and adequate blinding of global ordinal/quality-of-life outcome assessors (52.2%; Table 2). The blinding of primary personnel was high risk in the majority of studies (58.7%), likely because of the large number of trials focusing on device or protocol improvement interventions where blinding was expected to be challenging. Finally, the blinding of primary outcome assessors was low risk in the vast majority of trials (91.3%), due to the fact that most trials assessed relatively objective end points such as ROSC or survival, which are unlikely to

Table 1. General Characteristics of Contemporary RCTs for Cardiac Arrest Stratified by Type

Variable	Total (n=92)	OHCA (n=81)	IHCA (n=4)	OHCA/IHCA (n=7)
No. of subjects	64 309	60 447	724	3138
Median/study (IQR)	225.5 (119–703.75)	234 (120–750)	178 (142–217)	145 (104–460.5)
Average patient age, μ (σ)	65.6 (3.2)	65.5 (3.0)	66.2 (3.5)	66.2 (4.6)
Percent male, % (σ)	69.7 (8.6)	70.6 (8.4)	65.0 (5.5)	62.2 (8.9)
Witnessed arrest, % (σ)	74.0 (17.3)	72.7 (17.6)	81.0 (8.3)	86.4 (14.7)
Bystander CPR, % (σ)	41.1 (21.9)	40.1 (20.3)	N/A	45.3 (34.8)
Multicenter	61 (66.3)	55 (67.9)	2 (50.0)	4 (57.1)
United States only	18 (19.6)	17 (21.0)	1 (25.0)	0
Positive Outcome	25 (27.2)	23 (28.4)	2 (50.0)	0
Industry-sponsored	52 (56.5)	47 (58.0)	2 (50.0)	3 (42.9)
Publication year				
1995–1999	19 (20.7)	15 (18.5)	1 (25.0)	3 (42.9)
2000–2004	20 (21.7)	19 (23.5)	1 (25.0)	0
2005–2009	23 (25.0)	22 (27.2)	1 (25.0)	0
2010–2014	30 (32.6)	25 (30.9)	1 (25.0)	4 (57.1)
Type of intervention				
Drug	38 (41.3)	31 (38.3)	4 (100.0)	3 (42.9)
Device	39 (42.4)	36 (44.4)	0	3 (42.9)
Process improvement	15 (16.3)	14 (17.3)	0	1 (14.3)
Timing of intervention				
During cardiac arrest	74 (80.4)	68 (84.0)	1 (25.0)	5 (71.4)
Post cardiac arrest	15 (16.3)	13 (16.0)	0	2 (28.6)
During/post cardiac arrest	3 (3.3)	0	3 (75.0)	0
Initial arrest rhythm				
Pulseless VT/VF	19 (20.7)	19 (23.5)	0	0
PEA	7 (7.6)	6 (7.4)	0	1 (14.3)
Both	66 (71.7)	56 (69.1)	4 (100.0)	6 (85.7)

Continuous variables are reported as [μ (σ)] and categorical variables are reported as (n [%]). Most variables are categorical. Data for population characteristics provided for intervention group of RCTs. CPR indicates cardiopulmonary resuscitation; IHCA, in-hospital cardiac arrest; IQR, interquartile range; OHCA, out-of hospital cardiac arrest; PEA, pulseless electrical activity; RCT, randomized controlled trial; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 2. Risk of Bias Assessment of RCTs for Cardiac Arrest

Domain	Risk of Bias		
	Low	Unclear	High
Sequence generation (n=92)	32 (34.8)	55 (59.8)	5 (5.4)
Allocation concealment (n=92)	30 (32.6)	44 (47.8)	18 (19.6)
Blinding of primary personnel (n=92)	36 (39.1)	2 (2.2)	54 (58.7)
Blinding of primary outcome assessors (n=92)	84 (91.3)	8 (8.7)	0 (0)
Blinding of global ordinal/QOL outcome assessors (n=67)	29 (43.3)	35 (52.2)	3 (4.5)

Categorical variables are reported as (n [%]) Twenty-five studies did not report a global ordinal or quality-of-life (QOL) outcome. RCT indicates randomized controlled trial.

be misattributed regardless of outcome assessor blinding. Appendix Table II in the Data Supplement lists the risk of bias assessment for the 92 studies.

The most common outcome reported was ROSC (86 trials, 93.5%); 16 (17.4%) reported process measures, 77 (83.7%) reported survival to discharge, 20 (21.7%) reported 30-day to 6-month survival, and 22 (23.9%) reported survival beyond 6 months (Table 3). Fifty-three (57.6%) RCTs reported global ordinal outcomes, whereas 15 (16.3%) reported quality-of-life measures. The most common tool for the measurement of global ordinal outcomes was the cerebral performance category (or overall performance category; 43 of 53 [81.1%]). Eighteen (19.6%) studies reported other functional outcome measures, such as the modified mini-mental status examination. Notably, neurological assessments such as the NIHSS or FOUR score for comatose patients were not utilized in any of the RCTs in our systematic review. Twenty-one (25.9%) RCTs in OHCA evaluated survival beyond 6 months. None of the RCTs in IHCA and one of the mixed studies evaluated survival beyond 6 months. Twenty-three (28.4%) RCTs in OHCA reported a positive study outcome, whereas 2 (50.0%) of the 4 RCTs in IHCA and none of the mixed RCTs with both OHCA and IHCA achieved statistical significance with respect to their primary end point.

Factors Associated With RCTs Performed in the Past 5 Years

We found a total of 30 (32.6%) RCTs were performed in the past 5 years. We found several factors that were correlated with these more contemporary RCTs when compared with RCTs performed in the preceding 15 years; these are displayed in Table 4. Overall, we found a nonsignificant trend toward larger, multicenter studies in the past 5 years. Studies that focus on protocol improvements and postarrest care were significantly more common. However, we did not find an increase in RCTs of IHCA over time, nor did we find significant differences in other factors we evaluated, including industry funding, US-based studies, and survival assessments beyond ROSC.

Discussion

This systematic review brings together 20 years of resuscitation research on RCTs. It includes more than 90 RCTs with nearly 65 000 patients in total, making it to our knowledge the largest and most comprehensive systematic review of randomized investigations involving acute treatments studied in cardiac arrest. It highlights an overall paucity of RCTs in cardiac arrest and wide variation in their study design, settings, interventions, and reporting of outcomes. Overall, we found particularly important gaps in RCTs examining IHCA, protocol improvement interventions, postcardiac arrest care, and long-term survival and health status outcomes. Future RCTs could better target these knowledge gaps to improve our understanding of optimal management strategies for these high-risk patients.

The overall paucity of RCTs relative to the burden of disease in cardiac arrest is striking. In our systematic review, we found an average of 4.6 RCTs published annually representing just over 3200 patients enrolled each year. This could be considered a relatively modest investment in this disease process relative to its estimated burden in the general US population (≈535 000 combined OHCA and IHCA events occur in the United States annually with significant mortality).[1] For instance, this estimate represents ≈2.5 cardiac arrest RCTs performed per 10 000 cardiac arrest deaths annually for OHCA (and just 0.5 cardiac arrest RCTs performed per 10 000 cardiac arrest deaths annually for IHCA). This value lies within the same order of magnitude (6 published RCTs per 10 000 deaths per year) as described in a back-of-the-envelope calculation by Ornato et al[12] in a recent expert opinion piece evaluating the public health burden of cardiac arrest. This statistic becomes better placed in context when one considers that there are 25× to 86× the number of published RCTs per 10 000 deaths per year for heart failure, stroke, and myocardial infarction. Our findings reinforce the call by Ornato et al[12] for further clinical research into cardiac arrest with a particular emphasis on RCTs, as an opportunity exists to align research prioritization with the public health need.

Our systematic review identified several gaps that may help better define priorities in resuscitation research to fully realize this opportunity. For example, we discovered a striking paucity of studies examining IHCA. Only 4 studies in the past 20 years have focused on an exclusive IHCA cohort, and just an additional 7 studies examined both IHCA and OHCA (with most enrolling more patients with OHCA). Thus, RCTs in IHCA are clearly a fertile area for investigation given that IHCAs may make up as much as 40% of all cardiac arrest, and there are prominent pathogenic differences that distinguish it from OHCA.[5] The need for greater evidence for IHCA should be balanced against some evidence to suggest temporal progress in IHCA outcomes,[16] when compared with more modest improvements in OHCA over the same interval. This suggests that progress has been made in IHCA without the investment in RCTs perhaps through better patient selection or implementation of resuscitation care. Further investigation is needed related to the setting or type of intervention in cardiac arrest and the role of RCTs in improving the evidence base of therapies. Another prominent area that our review identified was a significant gap in the study of protocol interventions that evaluate the impact of systems changes in the management of cardiac arrest. Yet while the vast majority of RCTs have examined drugs and devices, we did note that many

Table 3. Measurement of Survival, Global Ordinal, and Quality-of-Life Outcomes in RCTs for Cardiac Arrest

Variable	Total (n=92)	OHCA (n=81)	IHCA (n=4)	OHCA/IHCA (n=7)
ROSC	86 (93.5)	75 (92.6)	4 (100.0)	7 (100.0)
Survival to hospital discharge	77 (83.7)	68 (84.0)	4 (100.0)	5 (71.4)
30-d to 6-mo survival	20 (21.7)	15 (18.5)	3 (75.0)	2 (28.6)
Long-term survival (>6 mo)	22 (23.9)	21 (25.9)	0	1 (14.3)
Neurologically intact survival	60 (65.9)	52 (65.0)	4 (100.0)	4 (57.1)
Quality-of-life outcomes	15 (16.3)	14 (17.3)	1 (25.0)	0
Global ordinal outcomes	53 (57.6)	45 (55.5)	4 (100.0)	4 (57.1)
CPC/OPC	43 (46.7)	38 (46.9)	2 (50.0)	3 (42.9)
GCS/GPCS	18 (19.6)	13 (16.0)	3 (75.0)	2 (28.6)
mRS	5 (5.4)	5 (6.2)	0	0
Other functional outcome	18 (19.6)	16 (19.8)	1 (25.0)	1 (14.3)

Categorical variables are reported as [n (%)]. CPC indicates cerebral performance category; GCS, Glasgow Coma Scale; GPCS, Glasgow-Pittsburgh Coma Scale; IHCA, in-hospital cardiac arrest; mRS, modified Rankin Scale; OHCA, out-of-hospital cardiac arrest; OPC, overall performance category; RCT, randomized controlled trial; and ROSC, return of spontaneous circulation.

more recent RCTs have begun to explore protocol interventions in the past 5 years. Finally, our study showed a dearth of interventions examining postcardiac arrest care. Yet this area has also changed in recent years with a push toward the increased evaluation of treatments instituted after ROSC has been achieved, likely driven by greater interest in therapeutic hypothermia.

Clinical trials in cardiac arrest treatments pose major logistical challenges because of the acuity and unexpected nature of its presentation, as well as heterogeneity of its patients, pathogeneses, and settings, including perceived barriers to informed consent. In 2011, the American Heart Association published a consensus statement specifically detailing the challenges for RCTs for cardiac arrest with respect to the selection of a meaningful primary outcome.[14] After extensive deliberation, it was clear that no single primary outcome would be appropriate for all studies of cardiac arrest with recommendations for pairing a time point and physiological condition to a specific question.[14] These recommendations highlight the challenges in the design and performance of RCTs in this area and the potential for great variation.[17]

An additional key finding from our study is that outcomes assessment continues to be limited. These results are consistent with a previously published systematic review, demonstrating the heterogeneity and lack of consistency in outcomes reporting in studies of cardiac arrest.[17] Like Whitehead et al[17] in previous work, we found no single outcome measure was universally or consistently assessed. Our data and these earlier reports continue to support the development of a standardized core outcome set through the Core Outcome Set for

Table 4. Trends in Select Characteristics of Cardiac Arrest RCTs From 1995 to 2014

Variable	1995–1999	2000–2004	2005–2009	2010–2014	*P* Value
Total no. of studies	19 (20.7)	20 (21.7)	23 (25.0)	30 (32.6)	
Any IHCA	4 (21.1)	1 (5.0)	1 (4.3)	5 (16.7)	0.338
Subjects*	10 347 (16.1)	4796 (7.5)	10 953 (17.0)	38 213 (59.4)	0.055
Multicenter	7 (36.8)	16 (80.0)	14 (60.9)	24 (80.0)	0.058
Geography (United States)	5 (26.3)	4 (20.0)	5 (21.7)	4 (13.3)	0.300
Industry funding	9 (47.4)	13 (65.0)	16 (69.6)	14 (46.7)	0.187
Survival assessment beyond ROSC	19 (100.0)	18 (90.0)	20 (87.0)	26 (86.7)	0.430
Drug	10 (52.6)	11 (55.0)	11 (47.8)	6 (20.0)	0.005
Device	9 (47.4)	7 (35.0)	9 (39.1)	14 (46.7)	0.564
Process improvement	0	2 (10.0)	3 (13.0)	10 (33.3)	0.004
Timing (during cardiac arrest)	18 (94.7)	17 (85.0)	19 (82.6)	20 (66.7)	0.025

Categorical variables are reported as (n [% total]). *P* value reported for logistic regression comparing variables during past 5 years (2010–2014) relative to values in previous intervals (1995–2009). IHCA indicates in-hospital cardiac arrest; RCT, randomized controlled trial; and ROSC, return of spontaneous circulation.

**P* value for subjects reported for comparison per 100 trial participants (% total out of 64 309).

Cardiac Arrest initiative (http://www.comet-initiative.org/studies/details/284). Our study also shows a striking lack of nonmortality-related patient outcomes, such as quality-of-life, and long-term assessments.[18] Even when assessed, the measurement was not optimal. We found that the most common nonsurvival assessment was the measurement of neurological outcomes using the cerebral performance category and done in the hospital setting. Although the cerebral performance category may be simple and easy to use, it is not patient-centered and serves as a coarse functional assessment at best.

A few pragmatic and financial concerns also merit consideration, particularly in regards to sample selection bias and the assessment of outcomes. A high proportion of witnessed arrest was reported in our systematic review (74%) when compared with contemporary epidemiological data from the 2014 Cardiac Arrest Registry to Enhance Survival (38% witnessed by bystander and 12% by EMS provider).[1] This highlights the ongoing challenges for RCTs in cardiac arrest to improve external validity through the recruitment of a more representative population. Moreover, as we strive to generate common outcome measures, some degree of outcome heterogeneity across studies may be expected. Distinct study-specific outcomes may be justified based on patient characteristics, study design, or trial intervention. In addition, comprehensive systematic assessment of long-term functional or quality-of-life outcomes is likely to be expensive and labor-intensive. As shown in a recent substudy of the Resuscitation Outcomes Consortium (ROC PRIMED), less than half of the OHCA survivors who were discharged could provide consent and be interviewed for a telephone assessment of neurological function, cognitive impairment, health-related quality of life, and depression ≤6 months after discharge.[19] The process proved to be not only tedious and expensive but also marked differences were observed in the cohort that was surveyed when compared with the cohort that could not provide consent because of death or loss to follow-up. Critically examining these sobering realities with regard to outcome and attempting to develop new approaches that address these challenges will be an important step as resuscitation science moves forward.

Our study should be interpreted with the following limitations. First, we did not have individual-level patient data for each study and could not address potential heterogeneity of treatment effects (drug, device, and protocol interventions). However, our goal was not to summarize such diverse types of treatments, which is beyond the capability of this type of review. Second, we chose to focus our attention on the acute treatment of cardiac arrest in individuals, and therefore, excluded large public health interventions, such as the Public Access Defibrillation Trial.[20] Third, the substantial heterogeneity of study designs is partly reflected by the complex nature of resuscitation research and the different types of treatments evaluated. This limited our ability to systematically measure the quality of RCTs, and so we independently collected aspects of study design shown to be useful in previous work for different medical conditions and elected not to provide a summary score to avoid confusion.[15,21,22] Finally, there is the possibility of publication bias in this field because of selective reporting, as we identified several small studies that were published and the rate of positive outcomes was remarkably high at 27%. We speculate that many negative studies are likely to have remained unreported in the literature, but the significant heterogeneity of interventions we assessed made it difficult to formally assess for this possibility. Although these types of RCTs are important to recognize as initial steps for evaluating highly exploratory treatments, they are unlikely to clinically affect most patients in any substantial way.

Despite these limitations, we believe our findings have important implications for how best to prioritize future work in cardiac arrest. We have noted that RCTs themselves are changing in size and scope with the emergence of a nonsignificant trend toward larger trials that involve multiple centers. Although recent data suggest RCTs may be increasingly targeting protocol interventions and postcardiac arrest care, there is no shift toward RCTs for IHCA or change in outcomes assessments. Finally, we found a limited number of new therapies proven effective in RCTs during the 20-year study period, suggesting that recent gains, however modest, may have been predominantly attributed to system-of-care optimization rather than new treatments.

Conclusions

Although cardiac arrest is a major public health concern worldwide, the extent and types of RCTs conducted in these high-risk patients have been largely unknown. We identified important gaps in research related to cardiac arrest treatments, with a paucity of RCTs with respect to the overall burden of disease in the general population. Particularly, striking gaps in knowledge include RCTs examining IHCA, protocol improvement, postcardiac arrest care, and long-term and quality-of-life outcomes. Although some of these characteristics are changing over time, greater knowledge of these gaps in research may help prioritize future work to improve care for these high-risk patients.

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Disclosures

None.

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Identifying Important Gaps in Randomized Controlled Trials of Adult Cardiac Arrest Treatments: A Systematic Review of the Published Literature

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SUPPLEMENTAL MATERIAL

Supplemental Appendix A. Selected Characteristics of Included Studies of RCTs of Adult Cardiac Arrest Treatments

Study Author/ Publication Year	Journal	Location of Arrest	Intervention Studied	Initial Arrest Rhythm	Number of Subjects	Single/Multicenter	Geographic Location	Timing of Intervention
Abu-Laban 2002[1]	*New England Journal of Medicine*	OHCA	100 mg IV tissue plasminogen activator versus placebo	PEA	233	Multicenter	Outside U.S.	During Cardiac Arrest
Abu-Laban 2006[2]	*Lancet*	OHCA	250 mg IV aminophylline versus placebo	Asystole or PEA refractory to epinephrine and atropine	971	Multicenter	Outside U.S.	During Cardiac Arrest
Allegra 2001[3]	*Resuscitation*	OHCA	2g IV magnesium sulfate versus placebo	Refractory VF	116	Multicenter	U.S.	During Cardiac Arrest
Arntz 2001[4]	*Circulation*	OHCA	Phased chest and abdominal compression-decompression (Lifestick™) CPR versus standard CPR	VF/PEA/Asystole	50	Multicenter	Outside U.S.	During Cardiac Arrest
Aufderheide 2005[5]	*Critical Care Medicine*	OHCA	Active versus sham ITD	Pulseless VT/VF/PEA/Asystole	230	Multicenter	U.S.	During Cardiac Arrest
Aufderheide 2011[6]	*Lancet*	OHCA	ACD-CPR + ITD versus standard CPR	Pulseless VT/VF/PEA/Asystole	1653	Multicenter	U.S.	During Cardiac Arrest
Aufderheide 2011[7]	*New England Journal of Medicine*	OHCA	Active versus sham ITD	Shockable VT/VF/ PEA/Asystole	8718	Multicenter	Inside/Outside U.S.	During Cardiac Arrest
Axelsson 2006[8]	*Resuscitation*	OHCA	Mechanical chest compression (LUCAS™) versus standard CPR	Pulseless VT/VF/PEA/Asystole	328	Multicenter	Outside U.S.	During Cardiac Arrest
Axelsson 2009[9]	*Resuscitation*	OHCA	Mechanical ACD-CPR (LUCAS™) versus standard CPR	Pulseless VT/VF/PEA/Asystole	126	Single	Outside U.S.	During Cardiac Arrest
Baker 2008[10]	*Resuscitation*	OHCA	3 min of CPR before first defibrillation versus immediate defibrillation	VF	202	Multicenter	Outside U.S.	During Cardiac Arrest

Baubin 1999[11]	*Resuscitation*	OHCA	Standard CPR followed by ACD-CPR versus ACD-CPR only versus standard CPR	Pulseless VT/VF	90	Single	Outside U.S.	During Cardiac Arrest
Bender 2007[12]	*Resuscitation*	OHCA	2 ml/kg/10 min IV hypertonic saline with HES versus IV HES alone	Pulseless VT/VF/PEA/Asystole	66	Single	Outside U.S.	During Cardiac Arrest
Berdowski 2010[13]	*Circulation: Arrhythmia and Electrophysiology*	OHCA	Use AEDs to perform postshock analysis and prompt pulse check versus resume CPR immediately after defibrillation	Pulseless VT/VF	136	Single	Outside U.S.	During Cardiac Arrest
Bernard 2002[14]	*New England Journal of Medicine*	OHCA	Therapeutic hypothermia (33°C) versus normothermia	VF	77	Multicenter	Outside U.S.	Post Cardiac Arrest
Bernard 2010[15]	*Circulation*	OHCA	Pre-hospital cooling versus cooling after hospital admission	VF	234	Multicenter	Outside U.S.	Post Cardiac Arrest
Bernard 2012[16]	*Critical Care Medicine*	OHCA	Pre-hospital cooling versus cooling after hospital admission	Asystole or PEA	163	Multicenter	Outside U.S.	Post Cardiac Arrest
Bertrand 2006[17]	*Intensive Care Medicine*	OHCA	Constant flow insufflation of oxygen versus mechanical ventilation	VF/PEA/Asystole	696	Multicenter	Outside U.S.	During/Post Cardiac Arrest
Bjelland 2012[18]	*Intensive Care Medicine*	OHCA	Propofol + remifentanil versus midazolam + fentanyl during therapeutic hypothermia (33-34°C for 24 hours)	Pulseless VT/VF/PEA/Asystole	59	Multicenter	Outside U.S.	Post Cardiac Arrest
Bohn 2011[19]	*Resuscitation*	OHCA	Extended feedback (addition of voice prompts during CPR) versus limited feedback (visual feedback + metronome only)	Pulseless VT/VF/PEA/Asystole	300	Single	Outside U.S.	During Cardiac Arrest
Bottiger 2008[20]	*New England Journal of Medicine*	OHCA	IV tenecteplase (weight-based dosing) versus placebo	Pulseless VT/VF/PEA/Asystole	1050	Multicenter	Outside U.S.	During Cardiac Arrest

Breil 2012[21]	*Resuscitation*	OHCA	2 ml/kg/10 min IV hypertonic saline with HES versus IV HES alone	Pulseless VT/VF/PEA/Asystole	203	Multicenter	Outside U.S.	During Cardiac Arrest
Callaway 2006[22]	*American Journal of Cardiology*	OHCA	40 IU Vasopressin versus placebo	VF/PEA/Asystole	325	Single	U.S.	During Cardiac Arrest
Castren 2010[23]	*Circulation*	OHCA	Intra-arrest, pre-hospital transnasal evaporative cooling (RhinoChill™) versus standard of care	VF/PEA/Asystole	194	Multicenter	Outside U.S.	Post Cardiac Arrest
Chardoli 2012[24]	*Chinese Journal of Traumatology - English Edition*	IHCA/OHCA	Echocardiography-integrated CPR versus standard CPR	PEA	100	Multicenter	Outside U.S.	During Cardiac Arrest
Choux 1995[25]	*Resuscitation*	OHCA	Repeated standard dose (1 mg IV) versus high dose (5 mg IV) of epinephrine	VF/EMD/Asystole	536	Single	Outside U.S.	During Cardiac Arrest
Debaty 2014[26]	*Intensive Care Med*	OHCA	Intra-arrest therapeutic hypothermia versus TH after hospital admission	Pulseless VT/VF/PEA/Asystole	245	Multicenter	Outside U.S.	During Cardiac Arrest
Dorian 2002[27]	*New England Journal of Medicine*	OHCA	5 mg/kg IV amiodarone + lidocaine placebo versus 1.5 mg/kg IV lidocaine + amiodarone placebo	Shock-resistant VF	347	Multicenter	Outside U.S.	During Cardiac Arrest
Dybvik 1995[28]	*Resuscitation*	OHCA	250 ml IV Tribonat™ (buffer solution) versus 250 ml of 0.9% IV normal saline	VF after first defibrillation attempt or Asystole	502	Single	Outside U.S.	During Cardiac Arrest
Fatovich 1997[29]	*Resuscitation*	OHCA	High dose (5 g) IV magnesium sulfate versus placebo	Pulseless VT/VF/Asystole	67	Single	Outside U.S.	During/Post Cardiac Arrest
Freese 2013[30]	*Circulation*	OHCA	Using AEDs with a VF waveform analysis algorithm versus standard shock-first protocol	VF	987	Multicenter	Inside/Outside U.S.	During Cardiac Arrest
Gueugniaud 1998[31]	*New England Journal of Medicine*	OHCA	Repeated (up to 15) high doses (5 mg IV each) versus standard doses (1 mg each) of epinephrine	VF/PEA/Asystole	3327	Multicenter	Outside U.S.	During Cardiac Arrest

Gueugniaud 2008[32]	*New England Journal of Medicine*	OHCA	1 mg IV epinephrine + 40 IU of IV vasopressin versus 1 mg IV epinephrine + saline placebo	VF after 3 failed defibrillation attempts/ PEA/Asystole	2894	Multicenter	Outside U.S.	During Cardiac Arrest
Hallstrom 2000[33]	*New England Journal of Medicine*	OHCA	Dispatcher-instructed bystander CPR by chest compression alone versus CPR by chest compression + mouth-to-mouth ventilation	Pulseless VT/VF/PEA/Asystole	520	Single	U.S.	During Cardiac Arrest
Hallstrom 2006[34]	*Journal of the American Medical Association*	OHCA	Automated load-distributing band (LDB-CPR) chest compression device versus manual CPR	Pulseless VT/VF/PEA/Asystole	767	Multicenter	Inside/Outside U.S.	During Cardiac Arrest
Hassan 2002[35]	*Emergency Medicine Journal*	OHCA	2 g IV magnesium sulfate versus placebo	VF/EMD/Asystole	105	Multicenter	Outside U.S.	Post Cardiac Arrest
Heard 2010[36]	*Resuscitation*	OHCA	Mechanical device for temperature management (Arctic Sun™) versus surface cooling with standard blankets + ice packs	Pulseless VT/VF/PEA/Asystole	64	Multicenter	U.S.	Post Cardiac Arrest
Holzer 2002 (HACA)[37]	*New England Journal of Medicine*	OHCA	Therapeutic hypothermia (32-34°C for 24 hours) versus normothermia	Pulseless VT/VF	275	Multicenter	Outside U.S.	Post Cardiac Arrest
Hostler 2011[38]	*British Medical Journal*	OHCA	Real-time audio and visual feedback during CPR versus standard CPR	Pulseless VT/VF/PEA/Asystole	1586	Multicenter	Inside/Outside U.S.	During Cardiac Arrest
Jacobs 2005[39]	*Emergency Medicine Australasia*	OHCA	90 seconds of CPR before defibrillation versus immediate defibrillation	Pulseless VT/VF	256	Single	Outside U.S.	During Cardiac Arrest
Jacobs 2011[40]	*Resuscitation*	OHCA	1 mg IV adrenaline versus saline placebo	Pulseless VT/VF/PEA/Asystole	534	Multicenter	Outside U.S.	During Cardiac Arrest
Jaffe 2004[41]	*American Journal of Cardiology*	OHCA	200 micrograms IV isoproterenol versus no isoproterenol	Asystole	79	Multicenter	Outside U.S.	During Cardiac Arrest

Jost 2010[42]	*Circulation*	OHCA	AED CPR protocol (1 minute CPR before 1st shock, shorter CPR interruptions, no stacked shocks) versus control protocol	VF	845	Single	Outside U.S.	During Cardiac Arrest
Kim 2007[43]	*Circulation*	OHCA	In-field cooling (up to 2 L of 4°C normal saline) versus standard care	VF/PEA/Asystole	125	Multicenter	U.S.	Post Cardiac Arrest
Kim 2014[44]	*Journal of the American Medical Association*	OHCA	Pre-hospital cooling (up to 2 L of 4°C normal saline) versus standard care	Pulseless VT/VF/PEA/Asystole	1359	Multicenter	U.S.	Post Cardiac Arrest
Knor 2011[45]	*Signa Vitae*	OHCA	10,000 units of intra-arrest IV heparin administration versus standard of care (no heparin)	Pulseless VT/VF/PEA/Asystole	63	Multicenter	Outside U.S.	During Cardiac Arrest
Kovoor 2005[46]	*Internal Medicine Journal*	OHCA	100 mg IV sotalol versus 100 mg IV lignocaine	VF and ≥ 4 defibrillatory monophasic shocks	129	Single	Outside U.S.	During Cardiac Arrest
Kudenchuk 1999[47]	*New England Journal of Medicine*	OHCA	300 mg IV amiodarone versus placebo	Pulseless VT/VF/PEA/Asystole	504	Multicenter	U.S.	During Cardiac Arrest
Kudenchuk 2006[48]	*Circulation*	OHCA	Transthoracic Incremental Monophasic versus Biphasic Defibrillation by Emergency Responders (TIMBER)	Pulseless VT/VF	168	Single	U.S.	During Cardiac Arrest
Laurent 2005[49]	*Journal of the American College of Cardiology*	OHCA	Isovolumic high-volume hemofiltration (200 mL/kg/hr over 8 hrs) +/-mild TH (32°C for 24 hrs) versus standard care	Pulseless VT/VF/PEA/Asystole	61	Multicenter	Outside U.S.	Post Cardiac Arrest
Longstreth 2002[50]	*Neurology*	OHCA	2g IV Mg sulfate or 10mg IV diazepam or both versus placebo	Pulseless VT/VF/PEA/Asystole	300	Single	U.S.	During Cardiac Arrest

Luiz 1996[51]	*Journal of Cardiothoracic and Vascular Anesthesia*	OHCA	ACD-CPR versus standard CPR	Pulseless VT/VF/PEA/Asystole	56	Single	Outside U.S.	During Cardiac Arrest
Ma 2012[52]	*Resuscitation*	OHCA	CPR first versus rhythm analysis for defibrillation first strategy	Pulseless VT/VF/PEA/Asystole	289	Single	Outside U.S.	During Cardiac Arrest
Mader 1999[53]	*Resuscitation*	OHCA	250 mg IV aminophylline versus placebo	Asystole	82	Single	U.S.	During Cardiac Arrest
Mader 2003[54]	*Academic Emergency Medicine*	OHCA	250 mg IV Aminophylline versus placebo	Atropine-resistant asystole	111	Multicenter	U.S.	During Cardiac Arrest
Mauer 1996[55]	*Resuscitation*	OHCA	ACD-CPR versus standard CPR	Pulseless VT/VF/PEA/Asystole	220	Single	Outside U.S.	During Cardiac Arrest
Mauer 1998[56]	*Resuscitation*	OHCA	Measuring end tidal CO_2 with ACD-CPR versus standard CPR	Pulseless VT/VF/PEA/Asystole	120	Single	Outside U.S.	During Cardiac Arrest
Mentzelopoulos 2009[57]	*Archives of Internal Medicine*	IHCA	120 IU IV vasopressin + 1 mg IV epinephrine + 40 mg IV methyl prednisolone versus 1 mg IV epinephrine + placebo during CPR and post-resuscitation hydrocortisone 300 mg IV for 7 days versus placebo	Pulseless VT/VF/PEA/Asystole	100	Single	Outside U.S.	During/Post Cardiac Arrest
Mentzelopoulos 2013[58]	*Journal of the American Medical Association*	IHCA	120 IU IV vasopressin + 1 mg IV epinephrine + 40 mg IV methyl prednisolone versus 1 mg IV epinephrine	Pulseless VT/VF/PEA/Asystole	268	Multicenter	Outside U.S.	During/Post Cardiac Arrest

			+ placebo during CPR and post-resuscitation hydrocortisone 300 mg IV for 7 days versus placebo					
Morrison 2005[59]	*Resuscitation*	OHCA	Rectilinear biphasic versus monophasic damped sine defibrillation waveforms (ORBIT)	Pulseless VT/VF	169	Multicenter	Outside U.S.	During Cardiac Arrest
Mukoyama 2009[60]	*Resuscitation*	OHCA	Maximum of 4 injections of either 40 IU IV vasopressin versus 1mg IV epinephrine immediately after ER arrival	Pulseless VT/VF/PEA/Asystole	336	Single	Outside U.S.	During Cardiac Arrest
Nielsen 2013[61]	*New England Journal of Medicine*	OHCA	Targeted temperature management at either 33°C versus 36°C	Pulseless VT/VF/PEA/Asystole	939	Multicenter	Outside U.S.	Post Cardiac Arrest
Oksanen 2007[62]	*Intensive Care Med*	OHCA	Strict (72-108 mg/dl) versus moderate (108-144 mg/dl) glucose control during first 48 hrs of ICU treatment	Pulseless VF	90	Multicenter	Outside U.S.	Post Cardiac Arrest
Olasveengen 2009[63]	*Journal of the American Medical Association*	OHCA	ACLS with IV drug administration versus ACLS without IV drug administration	Pulseless VT/VF/PEA/Asystole	851	Single	Outside U.S.	During Cardiac Arrest
Ong 2012[64]	*Resuscitation*	IHCA/OHCA	1mg IV adrenaline versus 40 IU IV vasopressin	Pulseless VT/VF/PEA/Asystole	727	Multicenter	Outside U.S.	During Cardiac Arrest

Patrick 1995[65]	*American Journal of Respiratory and Critical Care Medicine*	IHCA/OHCA	40 mg IV methoxamine versus 2mg IV epinephrine	Pulseless VT/VF/PEA/Asystole	145	Single	Outside U.S.	During Cardiac Arrest
Pittl 2013[66]	*Clinical Research in Cardiology*	IHCA/OHCA	Invasive cooling (Coolgard™) versus non-invasive surface cooling (Artic Sun ™)	Pulseless VT/VF/PEA/Asystole	80	Single	Outside U.S.	Post Cardiac Arrest
Plaisance 1997[67]	*Circulation*	OHCA	ACD-CPR versus standard CPR	Pulseless VT/VF/PEA/Asystole	512	Multicenter	Outside U.S.	During Cardiac Arrest
Plaisance 1999[68]	*New England Journal of Medicine*	OHCA	ACD-CPR versus standard CPR	Pulseless VT/VF/PEA/Asystole	750	Multicenter	Outside U.S.	During Cardiac Arrest
Plaisance 2004[69]	*Resuscitation*	OHCA	ACD-CPR + active ITD versus ACD-CPR + sham ITD	Pulseless VT/VF/PEA/Asystole	400	Multicenter	Outside U.S.	During Cardiac Arrest
Reades 2011[70]	*Annals of Emergency Medicine*	OHCA	Tibial intraosseous versus humoral intraosseous versus versus peripheral intravenous	Pulseless VT/VF/PEA/Asystole	182	Single	U.S.	During Cardiac Arrest
Rubertsson 2014[71]	*Journal of the American Medical Association*	OHCA	Mechanical chest compression and simultaneous defibrillation versus standard CPR (LINC)	Pulseless VT/VF/PEA/Asystole	2589	Multicenter	Outside U.S.	During Cardiac Arrest
Saissy 2000[72]	*Anesthesiology*	OHCA	Continuous insufflation of O2 versus IPPV in ACD-CPR	Pulseless VT/VF/PEA/Asystole	95	Multicenter	Outside U.S.	During Cardiac Arrest
Schmidbauer 2000[73]	*Resuscitation*	OHCA	High dose (5mg) versus standard dose (2.5mg) of endobronchial epinephrine	Pulseless VT/VF/PEA/Asystole	57	Single	Outside U.S.	During Cardiac Arrest

Schneider 2000[74]	*Circulation*	OHCA	AED with 150 J biphasic shocks versus 200-to-360 J monophasic shocks	VF	115	Multicenter	Outside U.S.	During Cardiac Arrest
Schwab 1995[75]	*Journal of the American Medical Association*	OHCA	ACD-CPR versus Standard CPR	VF/PEA/Asystole	860	Multicenter	U.S.	During Cardiac Arrest
Sherman 1997[76]	*Pharmacotherapy*	OHCA	High-dose (0.1 mg/kg) IV epinephrine versus standard-dose (0.01 mg/kg) IV epinephrine	VF or Asystole	140	Multicenter	U.S.	During Cardiac Arrest
Skogvoll 1999[77]	*Resuscitation*	OHCA	ACD-CPR versus Standard CPR	Pulseless VT/VF/PEA/Asystole	302	Single	Outside U.S.	During Cardiac Arrest
Smekal 2011[78]	*Resuscitation*	OHCA	Mechanical chest compressions (LUCAS™) versus Standard CPR	Pulseless VT/VF/PEA/Asystole	148	Multicenter	Outside U.S.	During Cardiac Arrest
Stiell 1996[79]	*Journal of the American Medical Association*	IHCA/OHCA	ACD-CPR versus Standard CPR	Pulseless VT/VF/PEA/Asystole	1784	Multicenter	Outside U.S.	During Cardiac Arrest
Stiell 2001[80]	*Lancet*	IHCA	40 IU IV Vasopressin versus 1mg IV epinephrine	Pulseless VT/VF/PEA/Asystole	200	Multicenter	Outside U.S.	During Cardiac Arrest
Stiell 2007[81]	*Circulation*	OHCA	Fixed lower energy (150-150-150 J) versus escalating higher energy (200-300-360 J)	Pulseless VT/VF patients with initial defibrillation by biphasic AED	221	Multicenter	Outside U.S.	During Cardiac Arrest
Stiell 2011[82]	*New England Journal of Medicine*	OHCA	Early-rhythm analysis (30 to 60 seconds CPR) versus delayed-rhythm analysis (180 seconds CPR)	Pulseless VT/VF/PEA/Asystole	9933	Multicenter	Inside/Outside U.S.	During Cardiac Arrest

Svensson 2010[83]	*New England Journal of Medicine*	OHCA	Compression-only CPR versus standard CPR	Pulseless VT/VF/PEA/Asystole	1276	Multicenter	Outside U.S.	During Cardiac Arrest
Takeda 2014[84]	*Resuscitation*	IHCA/OHCA	Pharyngeal cooling (saline 5°C into pharyngeal cuff for 120 min) versus standard of care	Pulseless VT/VF/PEA/Asystole	108	Multicenter	Outside U.S.	Post Cardiac Arrest
Thel 1997[85]	*Lancet*	IHCA	IV magnesium sulfate (2 g bolus followed by 8 g over 24 hours) versus placebo	Pulseless VT/VF/ EMD/Bradycardia/ Asystole	156	Single	U.S.	During/Post Cardiac Arrest
van Alem 2003[86]	*Resuscitation*	OHCA	Biphasic truncated exponential versus monophasic damped sine shocks	VF	120	Multicenter	Outside U.S.	During Cardiac Arrest
Vukmir 2006[87]	*American Journal of Emergency Medicine*	OHCA	1 mEq/kg IV sodium bicarbonate versus placebo	Pulseless VT/VF/PEA/Asystole	792	Multicenter	U.S.	During Cardiac Arrest
Wenzel 2004[88]	*New England Journal of Medicine*	OHCA	2 ampules of either 40 IU IV vasopressin versus 1 mg IV epinephrine	VF/PEA/Asystole	1186	Multicenter	Outside U.S.	During Cardiac Arrest
Wik 2003[89]	*Journal of the American Medical Association*	OHCA	CPR before defibrillation versus immediate defibrillation	Pulseless VT/VF	200	Single	Outside U.S.	During Cardiac Arrest
Wik 2014[90]	*Resuscitation*	OHCA	Integrated automated load-distributing band CPR versus standard CPR	Pulseless VT/VF/PEA/Asystole	4231	Multicenter	Inside/Outside U.S.	During Cardiac Arrest
Wolcke 2003[91]	*Circulation*	OHCA	ACD-CPR + ITD versus standard CPR	Pulseless VT/VF/PEA/Asystole	210	Multicenter	Outside U.S.	During Cardiac Arrest

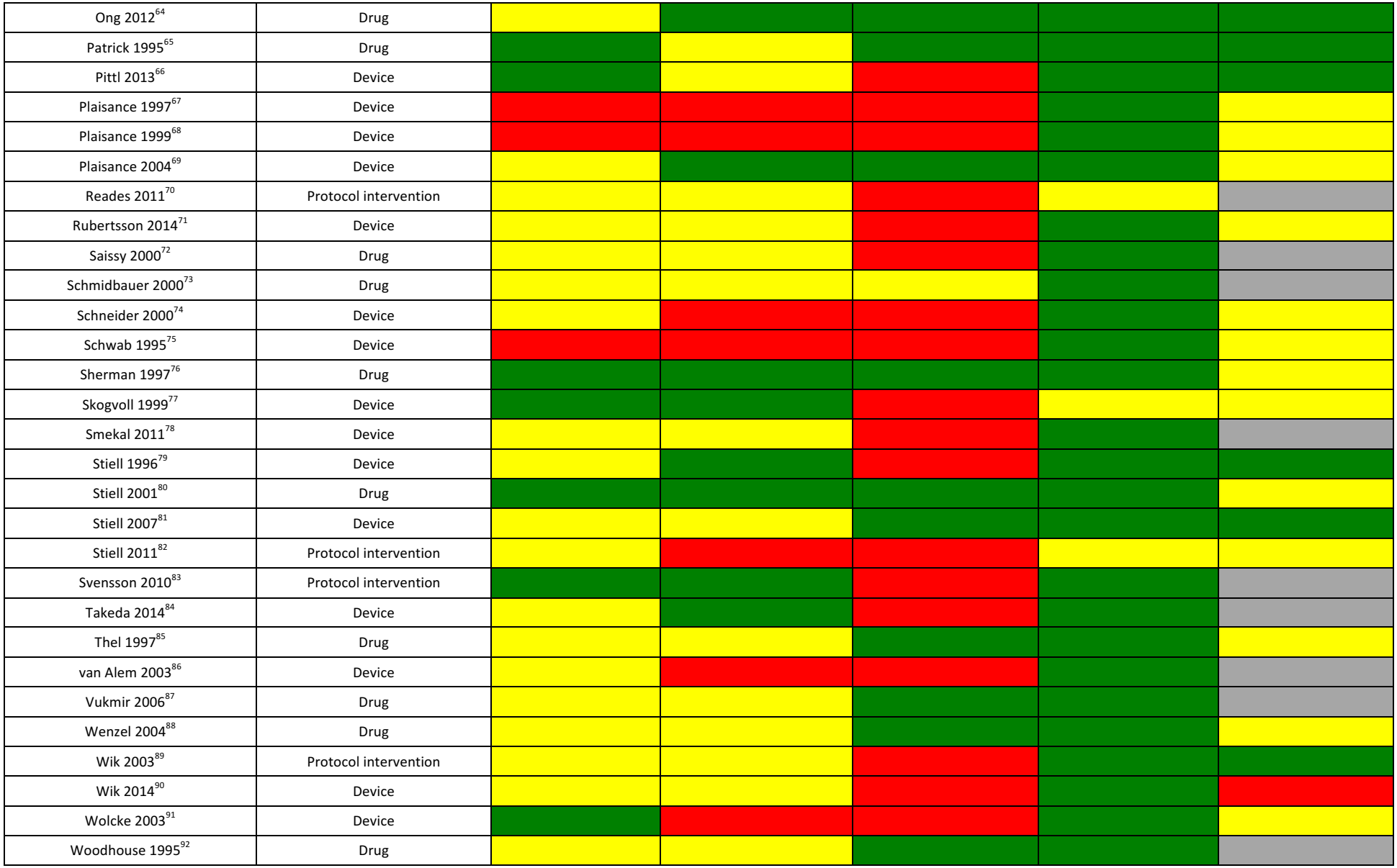
Woodhouse 1995[92]	*Resuscitation*	IHCA/OHCA	High-dose (10 mg IV) versus standard-dose (1 mg IV) adrenaline versus placebo	Pulseless VT/VF/EMD/Asystole	194	Single	Outside U.S.	During Cardiac Arrest

Supplementary Appendix Table A Abbreviations. ACD = active compression-decompression; AED = automated external defibrillator; CPR = cardiopulmonary resuscitation; EMD = electromechanical dissociation; IHCA = in-hospital cardiac arrest; Hydroxy ethyl starch; ITD = impedance threshold device; IV = intravenous; OHCA = out-of-hospital cardiac arrest; PEA = pulseless electrical activity; TH = therapeutic hypothermia; VT = ventricular tachycardia; VF = ventricular fibrillation; IPPV = intermittent positive pressure ventilation.

Supplemental Appendix B. Cochrane Collaboration Risk of Bias Assessment of Included Studies of RCTs of Adult Cardiac Arrest Treatments

Study Author/Publication Year	Trial Intervention	Sequence Generation	Allocation Concealment	Blinding of Primary Personnel	Blinding of Primary Outcome Assessors	Blinding of Global Ordinal/ Quality-of-Life Outcome Assessors
Abu-Laban 2002[1]	Drug					
Abu-Laban 2006[2]	Drug					
Allegra 2001[3]	Drug					
Arntz 2001[4]	Device					
Aufderheide 2005[5]	Device					
Aufderheide 2011[6]	Device					
Aufderheide 2011[7]	Device					
Axelsson 2006[8]	Device					
Axelsson 2009[9]	Device					
Baker 2008[10]	Protocol intervention					
Baubin 1999[11]	Device					
Bender 2007[12]	Drug					
Berdowski 2010[13]	Protocol intervention					
Bernard 2002[14]	Device					
Bernard 2010[15]	Device					
Bernard 2012[16]	Device					
Bertrand 2006[17]	Drug					
Bjelland 2012[18]	Drug					
Bohn 2011[19]	Protocol intervention					
Bottiger 2008[20]	Drug					
Breil 2012[21]	Drug					
Callaway 2006[22]	Drug					
Castren 2010[23]	Device					
Chardoli 2012[24]	Protocol intervention					
Choux 1995[25]	Drug					
Debaty 2014[26]	Device					
Dorian 2002[27]	Drug					
Dybvik 1995[28]	Drug					
Fatovich 1997[29]	Drug					

Freese 2013[30]	Protocol intervention					
Gueugniaud 1998[31]	Drug					
Gueugniaud 2008[32]	Drug					
Hallstrom 2000[33]	Protocol intervention					
Hallstrom 2006[34]	Device					
Hassan 2002[35]	Drug					
Heard 2010[36]	Device					
Holzer 2002 (HACA)[37]	Device					
Hostler 2011[38]	Protocol intervention					
Jacobs 2005[39]	Protocol intervention					
Jacobs 2011[40]	Drug					
Jaffe 2004[41]	Drug					
Jost 2010[42]	Protocol intervention					
Kim 2007[43]	Device					
Kim 2014[44]	Device					
Knor 2011[45]	Drug					
Kovoor 2005[46]	Drug					
Kudenchuk 1999[47]	Device					
Kudenchuk 2006[48]	Drug					
Laurent 2005[49]	Device					
Longstreth 2002[50]	Drug					
Luiz 1996[51]	Device					
Ma 2012[52]	Protocol intervention					
Mader 1999[53]	Drug					
Mader 2003[54]	Drug					
Mauer 1996[55]	Device					
Mauer 1998[56]	Device					
Mentzelopoulos 2009[57]	Drug					
Mentzelopoulos 2013[58]	Drug					
Morrison 2005[59]	Device					
Mukoyama 2009[60]	Drug					
Nielsen 2013[61]	Device					
Oksanen 2007[62]	Drug					
Olasveengen 2009[63]	Protocol intervention					



Ong 2012[64]	Drug					
Patrick 1995[65]	Drug					
Pittl 2013[66]	Device					
Plaisance 1997[67]	Device					
Plaisance 1999[68]	Device					
Plaisance 2004[69]	Device					
Reades 2011[70]	Protocol intervention					
Rubertsson 2014[71]	Device					
Saissy 2000[72]	Drug					
Schmidbauer 2000[73]	Drug					
Schneider 2000[74]	Device					
Schwab 1995[75]	Device					
Sherman 1997[76]	Drug					
Skogvoll 1999[77]	Device					
Smekal 2011[78]	Device					
Stiell 1996[79]	Device					
Stiell 2001[80]	Drug					
Stiell 2007[81]	Device					
Stiell 2011[82]	Protocol intervention					
Svensson 2010[83]	Protocol intervention					
Takeda 2014[84]	Device					
Thel 1997[85]	Drug					
van Alem 2003[86]	Device					
Vukmir 2006[87]	Drug					
Wenzel 2004[88]	Drug					
Wik 2003[89]	Protocol intervention					
Wik 2014[90]	Device					
Wolcke 2003[91]	Device					
Woodhouse 1995[92]	Drug					

Risk of bias is denoted as low risk of bias (green box), high risk of bias (red box), and unclear risk of bias (yellow box).
For the "blinding of global ordinal/quality-of-life outcome assessors" domain, a gray box was used to indicate studies that did not report the aforementioned outcomes.

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Supplemental Appendix C. Electronic Search Terms within the PubMed/EMBASE/Scopus Databases

PubMed

Therapy/Narrow[filter] AND (("heart arrest"[All Fields] OR "cardiac arrest"[All Fields]) OR ("Cardiopulmonary Resuscitation"[Mesh] OR "Heart Arrest"[Mesh])) AND ("1995/01/01"[PDAT] : "3000/12/31"[PDAT])

EMBASE *Note: eliminated keyword searches due to high search retrieval; all articles indexed so only EMTREE terms utilized*

'heart arrest'/exp AND 'resuscitation'/exp AND ([cochrane review]/lim OR [systematic review]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim) AND (1995:py OR 1996:py OR 1997:py OR 1998:py OR 1999:py OR 2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py)

Scopus *Note: filtered using adapted RCT strategy due to high search retrieval*

(TITLE-ABS-KEY ("cardiac arrest" OR "heart arrest" OR "cardiopulmonary resuscitation")) AND (TITLE-ABS-KEY ((clinical AND trial) OR “clinical trial*” OR random* OR “random allocation” OR “therapeutic use” OR “randomized controlled trial” OR (randomized AND controlled AND trial))) AND (LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000) OR LIMIT-TO (PUBYEAR , 1999) OR LIMIT-TO (PUBYEAR , 1998) OR LIMIT-TO (PUBYEAR , 1997) OR LIMIT-TO (PUBYEAR , 1996) OR LIMIT-TO (PUBYEAR , 1995))

Supplemental Appendix D. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S.A. D
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4,5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5,6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5,6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-9,19, 21-23, S.A. A
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, 20, S.A. B
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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