Received: 20 May 2024 | Revised: 23 July 2024 | Accepted: 1 October 2024

DOI: 10.1002/emp2.13334

JACEP OPEN
JOURNAL OF THE AMERICAN COLLEGE OF EMERGENCY PHYSICIANS OPEN
A GLOBAL JOURNAL OF EMERGENCY MEDICINE
WILEY

SYSTEMATIC REVIEW

Cardiology

Evaluating the current breadth of randomized control trials on cardiac arrest: A scoping review

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Abstract

Objectives: Despite the significant disease burden due to cardiac arrest, there is a relative paucity of randomized controlled trials (RCTs) to inform definitive management. We aimed to evaluate the current scope of cardiac arrest RCTs published between 2015 and 2022.

Methods: We conducted a search in October 2023 of MEDLINE, Embase, and Web of Science for cardiac arrest RCTs. We included trials published between 2015 and 2022 enrolling human subjects suffering from non-traumatic cardiac arrest. Descriptive statistics were reported and the Mann Kendall test was used to evaluate for temporal trends in the number of trials published annually.

Results: We identified 1764 unique publications, 87 RCTs were included after title/abstract and full-text review. We found no significant increase in trials published annually (eight in 2015 and 16 in 2022, $p = 1.0$). Geographic analysis of study centers found 31 countries represented; Denmark ($n = 13$, 15%) and the United States ($n = 9$, 10%) conducted the majority of trials. Nearly all trials included adults ($n = 84$, 97%)

and few included children ($n = 9$, 10%). The majority of trials focused on out-of-hospital cardiac arrest ($n = 62$, 71%). Thirty-eight (44%) trials used an intervention characterized as a *process improvement*; 28 (32%) interventions were characterized as a *drug* and 20 (23%) as a *device*. Interventions were implemented with similar frequency in the prehospital (33%) and intensive care unit (38%) setting, as well as similarly between the intra-arrest (53%) and post-arrest (46%) periods. Twenty (27%) trials selected a primary outcome of survival at ≥ 28 days.

Conclusions: Publication of cardiac arrest RCTs remained constant between 2015 and 2022. We identified significant gaps including a lack of trials examining in-hospital cardiac arrest and pediatric patients.

KEYWORDS
clinical trials as topic, heart arrest, out-of-hospital cardiac arrest, random allocation

1 | INTRODUCTION

1.1 | Background

Cardiac arrest represents a significant public health burden throughout the world. There are approximately 294,000 EMS-treated out-of-hospital cardiac arrests (OHCA) and 292,000 in-hospital cardiac arrests (IHCA) among adults in the United States annually, and similarly high incidence of OHCA and IHCA worldwide.[1–5] For cardiac arrest cases, the rate of survival is approximately 9% for OHCA and 26% for IHCA, and has only increased incrementally over the past decade.[1–3] Cardiac arrest has been associated with similar disease burden as measured in disability-adjusted life years (DALYs) compared with other leading health conditions such as ischemic heart disease and stroke.[6]

1.2 | Importance

The randomized controlled trial (RCT) has long been considered the gold standard to evaluate therapeutic interventions[7]; yet, a relative paucity of RCTs exist to inform the definitive management of in-hospital and out-of-hospital cardiac arrest relative to the large public health burden.[8] There are recognized gaps in resuscitation knowledge as a result.[9] A prior Institute of Medicine report in 2015 called for increased research into cardiac arrest resuscitation and brought attention to a substantial lack of funding for cardiac arrest in comparison to diseases with significantly less disease burden.[10] This corroborated the results of two studies that systematically reviewed the scope of RCTs between 1995 and 2014 evaluating cardiac arrest treatments, and noted a publication rate of 4.6 RCTs annually and a wide variation in study designs, settings, interventions, and reported outcomes.[8,11] The evolution of cardiac arrest care and longitudinal improvements in survival have been slowed by this mismatch between the high disease burden associated with cardiac arrest and relatively few clinical trials to inform care.[3,12]

1.3 | Goals of this investigation

Since the last major systematic review on RCTs of adult cardiac arrest treatments by Sinha et al. in 2016, the subsequent trajectory of RCTs of cardiac arrest treatments is unknown. Additionally, the scope of RCTs focusing specifically on pediatric patients is not well described. This scoping review of RCTs for IHCA and OHCA interventions between 2015 and 2022 aims to evaluate what progress has been made in RCTs studying cardiac arrest treatments since the last major review in 2016, and to identify gaps in the current scope of cardiac arrest research to inform the development of future research priorities and trials.

2 | METHODS

2.1 | Study design and search strategy

We performed a systematic search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews guidelines[13] (PRISMA-ScR; Supporting Information A) of three databases including MEDLINE, Embase, and Web of Science. We conducted our search in October 2023 and targeted studies published between 2015 and 2022 that enrolled human subjects of randomized trials and evaluated patients with non-traumatic cardiac arrest. Search terms are detailed in Supporting Information B.

2.2 | Selection of studies

One of five independent reviewers screened the unique titles and abstracts for potential study inclusion after de-duplication (C.G., K.W., L.F., M.K., and J.T.). We began by having all reviewers examine the same 100 titles and abstracts, and we then calculated a Fleiss' kappa to assess interrater reliability after this initial screening. The remaining titles and abstracts were then reviewed by at least two out of four

reviewers (C.G., K.W., L.F., and M.K.). We resolved any conflicting decisions during the title and abstract review through discussion and with a third reviewer (J.T.) if needed.

Studies met inclusion criteria if they were original research studies that randomized human subjects who experienced non-traumatic cardiac arrest into an intervention and control group to test the effect of an intervention. The study investigators must have initiated the intervention during or within 24 h of cardiac arrest. We excluded studies that focused on interventions specifically for traumatic cardiac arrest, primary prevention (eg, implantable cardiac devices), channelopathies and arrythmias, and cardioplegia. We also excluded simulation studies, cadaver studies, and pilot studies with <50 subjects. If multiple reports were published from a single dataset (eg, pre-planned subanalysis, interim analysis, and post hoc analysis), only the initial trial was included. Furthermore, we included published pilot and feasibility studies with ≥50 subjects that were associated with published trials only if the sample population was not included in the primary trial or if the primary trial was not published during the search period. Our inclusion criteria mirrored the previously published criteria for the systematic review of cardiac arrest RCTs.[8]

Two independent reviewers (J.T. and L.F.) evaluated all full-text publications based on the same screening criteria as above after title and abstract review. We recorded reasons for exclusion after full-text review, and we resolved disagreements through consensus agreement and with a third reviewer (K.W.) if needed. We performed the screening and full-text review using the web-based application Rayyan (Rayyan Systems Inc.). Citations of included trials were not reviewed for additional studies not located in the primary search.

2.3 | Data extraction and synthesis

Two independent reviewers extracted data (J.T. and L.F.) using a standardized form in Excel (version 16.66.1; Microsoft Corp.). We cross-checked data after both independent reviewers extracted it; any disagreements regarding extracted values were resolved through consensus agreement or with a third reviewer (K.W.). Variables extracted included title, authors, publication year, country of each study site, number of study centers (eg, single or multicenter), pilot or feasibility study (as self-reported by the trial authors), single or double-blinded, level of randomization (eg, individual or cluster), unit of randomization (eg, patient, paramedic, hospital, etc), population demographic (eg, ≥18years, <18 years, or both), location of cardiac arrest (eg, IHCA, OHCA, IHCA + OHCA), study intervention, timing of intervention (eg, intra-arrest, post-arrest), location where intervention was initiation, primary outcome, total sample size, start and end dates of patient enrollment, industry funding or sponsorship (as self-reported by the trials authors), and if the study was terminated early. If a study focused on cardiac arrest in which the index case occurred while the patient was in the ED, this was considered an IHCA. Additionally, if the study examined a specific subset of cardiac arrest patients, these data were also extracted including initial rhythm (eg, shockable, non-shockable), arrest witnessed status, and presumed cardiac etiology.

Two study investigators (J.T. and L.F.) classified data on the study intervention into four categories. We resolved disagreements through consensus agreement and with a third reviewer (K.W.). These categories included decision support, device, drug, or process improvement. We defined *decision support* as any intervention which tested the effect of a system or technology that supported operator decision making, *device* as any intervention testing the effect of a device compared with standard care (eg, mechanical cardiopulmonary resuscitation [CPR] device vs standard CPR), and *drug* as any intervention testing the effect of a pharmacologic management versus standard care. We defined *process improvement* as an intervention that tested the effect of a change in timing or approach of a treatment (eg, therapeutic hypothermia vs. normothermia post-cardiac arrest).

2.4 | Data analysis

We calculated descriptive statistics including frequencies and percentages for categorical variables, and median and interquartile range (IQR) for continuous variables. The Mann Kendall test was used to evaluate for temporal trends in the number of published trials. Pilot and feasibility studies with ≥50 patients and no overlapping data with primary trials were included in the overall analysis; these studies also require significant investment of time and funding and, in isolation, have the potential to contribute to knowledge surrounding cardiac arrest care. However, we did not include these trials in the analysis of study characteristics over time or of primary outcomes due to inherent design differences when compared to the primary trial. To evaluate for significant changes in study characteristics over time, we combined trial publication years into 4-year increments and a logistic regression model was used. This model aimed to evaluate if there were significant longitudinal changes in the study characteristics of trials published during the search period. We selected publication in 2019–2022 as the dependent variable and assessed the odds that a given independent variable would be more likely to be present during 2019–2022 than 2015–2018. Independent variables were independently assessed; these included if the trial was multicenter, patient demographics, location of cardiac arrest, type of intervention, and timing of the intervention. We considered a p-values <0.05 to be statistically significant. All analyses were conducted via R software (R Foundation for Statistical Computing, version 4.3.3).

3 | RESULTS

We identified a total of 1764 unique publications (Figure 1). After title and abstract review (Fleiss' kappa 0.75), 142 studies remained; after full text review, we identified 87 RCTs for inclusion with a median 9.5 trials per year. There was no significant increase in trials published annually during the search period; eight trials were published in 2015 and 2016 in 2022 ($p = 1.0$) (Figure 2). Among included trials, we identified 12 (14%) pilot or feasibility studies. Geographic analysis of study centers found 31 countries represented; we noted that a majority

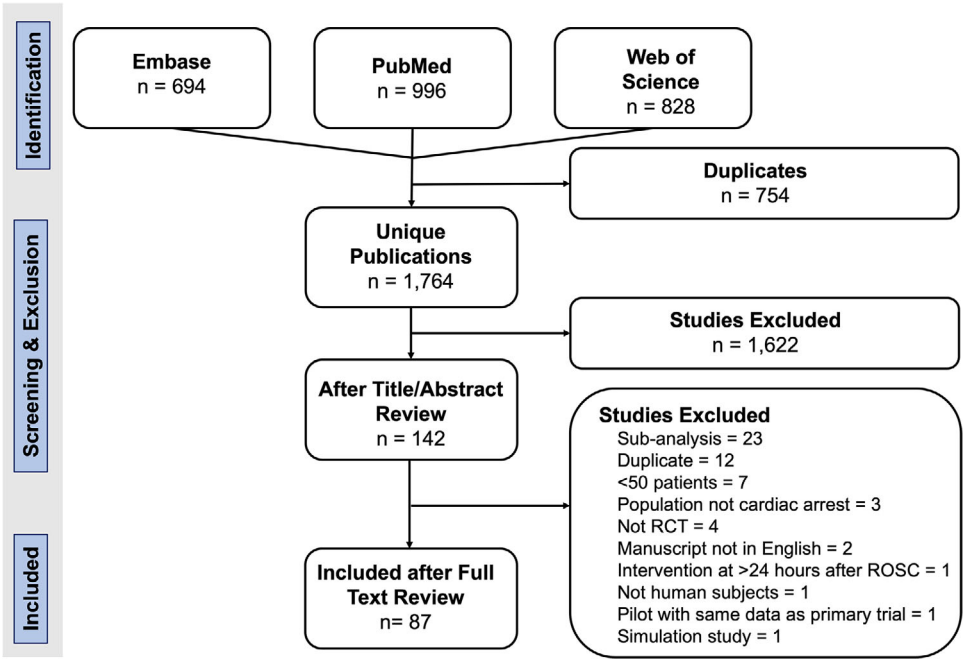

FIGURE 1 Flow diagram for studies included from 2015 to 2022. RCT, randomized controlled trial; ROSC, return of spontaneous circulation.

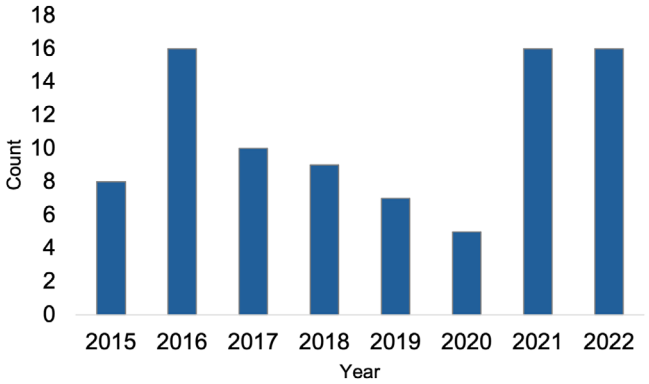

FIGURE 2 Frequency of randomized controlled trials published by year. There was no significant increasing or decreasing trend ($p = 1$).

($n = 74$, 85%) were conducted within a single country (Figure 3). Denmark had the highest number of trials ($n = 13$, 15%) followed by the United States ($n = 9$, 10%), UK ($n = 9$, 10%), France ($n = 9$, 10%), and Germany ($n = 7$, 8%).

Complete descriptive statistics are reported in Table 1. We found that most trials were multicenter ($n = 55$, 63%), single-blinded ($n = 67$, 77%), and conducted randomization at the level of the individual patient ($n = 72$, 83%). Nearly all trials included adults ($n = 84$, 97%) and few included children ($n = 9$, 10%). The majority of trials focused on OHCA ($n = 62$, 71%) and included patients irrespective of initial rhythm, witnessed status, or presumed cardiac etiology. The trial intervention was initiated with similar proportions between the intra-arrest and post-arrest periods and was most often categorized as a *process improvement* ($n = 38$, 44%). The majority of interventions were initiated in the intensive care unit ($n = 34$, 39%) or prehospital ($n = 29$, 33%) setting. The median sample size was 271 patients (IQR 90, 850) and the median trial length was 29 months (IQR 16, 45).

Descriptive statistics over time are reported for select study characteristics in Table 2. No study characteristic assessed was more likely to be present in 2019–2022 as compared to 2015–2018.

Descriptive statistics for the primary trial outcomes are reported in Table 3. Twenty (27%) trials selected a primary outcome of survival at ≥28 days, with one trial[14] evaluating survival at >180 days. Fifteen (21%) trials evaluated neurologically intact survival.

See Supporting Information C for a complete list of all trials included.

3.1 | Limitations

Our findings should be interpreted with the following limitations. First, our study reviewed only RCTs and we did not evaluate the scope of prospective, non-randomized studies, which also contribute to guidelines for cardiac arrest care.[15] Second, RCT intervention types (ie, *device*, *process improvements*, etc) were labeled by subjective reviewer assessment. While the categories were similar to those reported by Sinha et al,[8] potential differences in reviewer judgement are important to consider when evaluating direct comparisons between the studies. To address potential inconsistency, we brought together multiple reviewers to provide consensus for any disagreements during categorization of intervention type. Third, we noted only "substantial agreement" between all reviewers; the reason for most discrepancies stem from the difficulty identifying the numerous published subanalyses following each primary trial. Nevertheless, we feel that the studies included in this review are largely reflective of RCTs during the

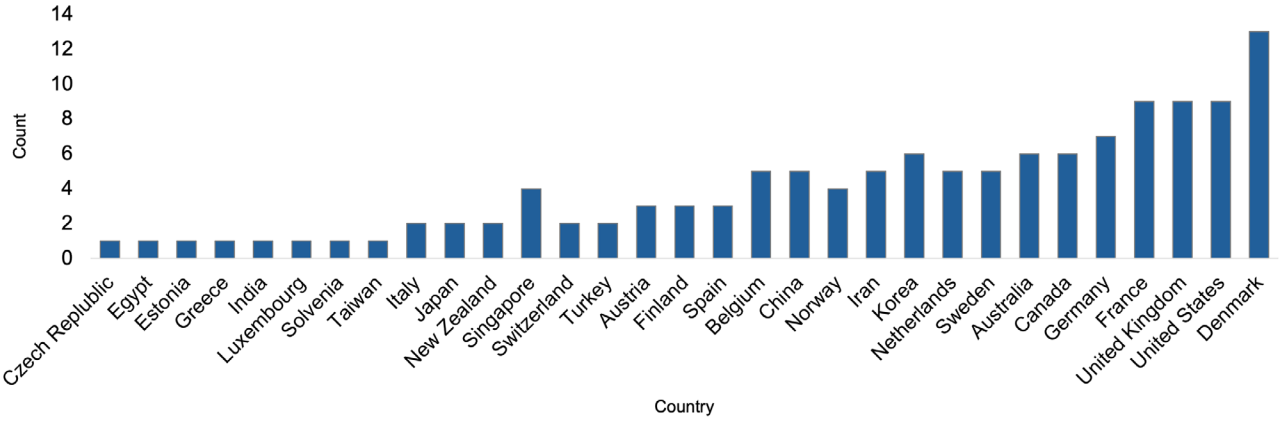

FIGURE 3 Frequency randomized controlled trials by country participation. *Note*: In multinational collaborations, study sites are represented individually in the counts for each country.

TABLE 1 Descriptive statistics.

	Total ($n = 87$), n (%)	IHCA ($n = 15$), n (%)	IHCA + OHCA ($n = 11$), n (%)	OHCA ($n = 61$), n (%)
Pilot or feasibility study[a]	12 (14)	1 (7)	0 (0)	11 (18)
Number of sites				
Multicenter	55 (63)	8 (53)	6 (55)	41 (67)
Single center	32 (37)	7 (47)	5 (45)	20 (33)
Double blinded	20 (23)	4 (27)	1 (9)	15 (25)
Level of randomization				
Individual	72 (83)	15 (100)	72 (655)	72 (118)
Cluster	15 (17)	0 (0)	15 (136)	15 (25)
Unit of randomization				
Day or week	2 (2)	0 (0)	2 (18)	0 (0)
Dispatcher	1 (1)	0 (0)	0 (0)	1 (2)
EMS service or provider	12 (14)	0 (0)	0 (0)	12 (20)
Hospital	1 (1)	0 (0)	0 (0)	1 (2)
Patient	70 (80)	15 (100)	8 (73)	47 (77)
Physician	1 (1)	0 (0)	1 (9)	0 (0)
Demographics				
Adults (≥18 years)	84 (97)	15 (100)	8 (73)	61 (100)
Children (<18 years)	9 (10)	0 (0)	3 (27)	6 (10)
Both	7 (8)	0 (0)	1 (9)	6 (10)
Initial rhythm				
All	72 (83)	14 (93)	9 (82)	49 (80)
Non-shockable	4 (5)	1 (7)	1 (9)	2 (3)
Shockable	11 (13)	0 (0)	1 (9)	10 (16)
Witnessed only	13 (15)	3 (20)	0 (0)	10 (16)
Presumed cardiac etiology only	22 (25)	0 (0)	1 (9)	21 (34)
Type of intervention				
Decision support	1 (0)	(0)	(0)	(0)
Device	20 (23)	6 (40)	3 (27)	11 (18)
Drug	28 (32)	6 (40)	5 (45)	17 (28)
Process improvement	38 (44)	3 (20)	3 (27)	32 (52)

(Continues)

TABLE 1 (Continued)

	Total ($n = 87$), n (%)	IHCA ($n = 15$), n (%)	IHCA + OHCA ($n = 11$), n (%)	OHCA ($n = 61$), n (%)
Timing of intervention				
Intra-arrest	46 (53)	11 (73)	4 (36)	31 (51)
Intra-arrest/post-arrest	1 (1)	1 (7)	0 (0)	0 (0)
Post-arrest	40 (46)	3 (20)	7 (64)	30 (49)
Location of intervention initiation				
Catheterization lab	5 (6)	0 (0)	0 (0)	5 (8)
Dispatch	2 (2)	0 (0)	0 (0)	2 (3)
Emergency department	9 (10)	3 (20)	3 (27)	3 (5)
Intensive care unit	33 (38)	7 (47)	5 (45)	21 (34)
In-hospital	5 (6)	5 (33)	0 (0)	0 (0)
Multiple	4 (5)	0 (0)	3 (27)	1 (2)
Prehospital	29 (33)	0 (0)	0 (0)	29 (48)
Sample size, median (IQR)	342.5 (90, 849.5)	127 (85, 298)	172 (76.5, 241)	405 (123, 1174)
Study length (months), median (IQR)	28.8 (16, 44.5)	15.2 (9.5, 23.6)	40.1 (19, 65.6)	32.5 (19.9, 44.5)
Industry sponsored/funded	17 (20)	2 (13)	2 (18)	13 (21)
Study terminated early	4 (5)	0 (0)	0 (0)	4 (7)

Abbreviations: EMS, emergency medical services; IHCA, in-hospital cardiac arrest; IQR, interquartile range; OHCA, out-of-hospital cardiac arrest.
[a]Pilot and feasibility studies were included if they had ≥50 patients and if these patients were not included the subsequent primary trial publication.

TABLE 2 Trial characteristics by 2-year increments.

	2015–2016 ($n = 22$), n (%)	2017–2018 ($n = 14$), n (%)	2019–2020 ($n = 9$), n (%)	2021–2022 ($n = 30$), n (%)	p-Value
Multicenter	16 (73)	11 (79)	8 (89)	14 (47)	0.36
Demographic included					
Adults (≥18 years)	22 (100)	12 (86)	9 (100)	29 (97)	0.99
Children (<18 years)	2 (9)	4 (29)	0 (0)	3 (10)	0.76
Both	3 (14)	2 (14)	0 (0)	2 (7)	0.43
Study population					
Any IHCA	7 (32)	4 (29)	4 (44)	10 (33)	0.94
Any OHCA	19 (86)	13 (93)	7 (78)	22 (73)	0.45
Type of intervention					
Decision support	0 (0)	0 (0)	0 (0)	1 (3)	0.99
Device	8 (36)	3 (21)	3 (33)	4 (13)	0.32
Drug	5 (23)	5 (36)	0 (0)	10 (33)	0.12
Process improvement	9 (41)	6 (43)	3 (33)	15 (50)	0.79
Timing of intervention					
Intra-arrest	14 (64)	8 (57)	4 (44)	16 (53)	0.36
Intra-arrest/post-arrest	0 (0)	0 (0)	0 (0)	1 (3)	0.99
Post-arrest	8 (36)	6 (43)	5 (56)	13 (43)	0.44

Note: Twelve pilot studies were excluded from this table.
Abbreviations: IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest.

search period. Lastly, it is possible that the COVID-19 pandemic may have influenced our results as there were relatively few trials published during 2020; however, the number of trials increased significantly in 2021 and as such, the extent of impact is difficult to ascertain.

4 | DISCUSSION

This scoping review of recent RCTs of cardiac arrest did not find a significant increase in the number of trials published annually. We

TABLE 3 Trial primary outcomes.

	Total ($n = 75$), n (%)	IHCA ($n = 14$), n (%)	IHCA + OHCA ($n = 11$), n (%)	OHCA ($n = 50$), n (%)
ROSC	14 (19)	8 (57)	1 (9)	6 (12)
Survival to hospital discharge	5 (7)	0 (0)	0 (0)	5 (10)
Survival at 28–180 days	19 (26)	2 (14)	2 (18)	15 (30)
Survival at >180 days	1 (1)	0 (0)	0 (0)	1 (2)
Neurologically intact survival	15 (21)	1 (7)	2 (18)	12 (24)
Used CPC	12	0	2	10
Used mRS	3	1	0	2

Note: Twelve pilot studies were excluded from this table.
Abbreviations: CPC, cerebral performance category; IHCA, in-hospital cardiac arrest; mRS, modified Rankin scale; OHCA, out-of-hospital cardiac arrest; ROSC, return of spontaneous circulation.

observed a majority of trials focused on adult patients and OHCA, with relative gaps in trials focusing on pediatric patients or IHCA. Most trial interventions focused on *process improvements* as opposed to *devices* or *drugs*. For study primary outcomes of major trials, we found that over one-half focused on survival or neurologically intact survival. Our results build upon the prior findings of Sinha et al who systematically reviewed RCTs for cardiac arrest between 1995 and 2014.[8]

Comparison of trial design characteristics from our search with the results of Sinha et al. provide insight into the trajectory of cardiac arrest research.[8] Sinha et al. found an increasing trend in cardiac arrest RCT publications between 1995 and 2014;[8] however, we did not note a continuation of this observed trend between 2015 and 2022. The annual volume of publications in our review was higher than previously published; this may in part be due to our inclusion of trials that included pediatric patients. Additionally, we found persistently low numbers of studies of IHCA or focused on non-shockable rhythms in as compared to 1995–2014. IHCA accounts for nearly 50% of all cardiac arrests in the United States annually; nonetheless, only 33% of all trials published in 2021 and 2022 included any IHCA patients, which may hinder generalizability of the results of those trials.[2] Likewise, the majority of cardiac arrest patients have an initial non-shockable rhythm; however, only 5% of all trials focused exclusively on this cardiac arrest cohort.[1] Furthermore, we found a larger proportion of trials between 2015 and 2022 focused more post-cardiac arrest care as compared with intra-arrest care, and the interventions more frequently characterized as *process improvement*, as opposed to *devices* or *drugs*. The focus on *process improvements* may reflect a lack of promising new *device* or *drug* interventions. Interestingly, the increased focus on post-arrest care and *process improvement* interventions in our review filled gaps and aligned with priorities in cardiac arrest research identified by Panchal et al.[9]

This review further characterized primary outcomes to provide an understanding of the evolution of cardiac arrest trial design. We found that most large trials selected primary outcomes that assessed long term survival and neurologically intact survival. This aligns with a 2018 International Liaison Committee on Resuscitation Advisory Statement on core outcomes for cardiac arrest trials.[16] Contrary to these guidelines, however, we did not identify any studies in this review that selected health-related quality of life measures as a primary outcome (eg, activities of daily living or health-related quality of life assessments). Our results could not be directly compared to those of Sinha et al as they extracted and analyzed all outcomes (ie, primary and secondary); they found that ROSC was the most common outcome in 94% of trials.[8] We chose not to extract secondary outcomes given the sample size in some trials may not have been specifically powered to address these additional outcomes. Overall, focusing on survival outcomes is crucial for adequately understanding the clinical impact of cardiac arrest trials.

This review identified a relative paucity of cardiac arrest trials in comparison to trials for other diseases with similar burden. In the United States, the rate of OHCA disability-adjusted life years (DALY) per 100,000 individuals has been documented at 1347; in comparison, stroke DALY per 100,000 individuals was 980.[6] While OHCA DALY exceeded stroke DALY, there have been significantly fewer published RCTs for OHCA compared to stroke.[6] Notably, a prior meta-analysis evaluating large stroke RCTs found approximately 20 RCTs per year between 2004 and 2018.[17] Comparatively, this study found an average of 10.8 RCTs per year. While both acute disease processes represent time-sensitive emergencies requiring significant EMS resources and hospital infrastructure to coordinate multi-disciplinary care, there have been significantly fewer cardiac arrest trials compared to stroke.

Factors contributing to this relative paucity of cardiac arrest trials is likely multifactorial. A primary driving cause is likely a lack of funding for large-scale investigations.[18,19] A 2015 review of National Institutes of Health (NIH) funding reported that only 0.19% of the total NIH budget was invested in cardiac arrest research while 1.4% and 5.9% were invested in stroke and heart disease, respectively.[19] Additional logistical challenges include recruiting and training sufficient EMS agency participants, prehospital randomization, linking EMS reports with hospital outcome data, and the heterogeneity of regional EMS protocols.[20–22] The significant disease burden associated with cardiac arrest and relatively few trials published annually, together, represent an important disconnect in current research prioritization. It is critical that we improve cardiac arrest research infrastructure and establish cardiac arrest as a research priority commensurate with the increasingly large public health burden it addresses. Failure to address these issues will likely impede advancement and innovation in cardiac arrest care and slow progress toward improving patient outcomes.

In summary, we identified a comparative lack of published RCTs addressing cardiac arrest between 2015 and 2022 despite the significant public health threat and disease burden associated with cardiac arrest. We found significant gaps including a lack of trials examining IHCA or pediatric patients, as well as patients with non-shockable initial rhythms. Altogether, our findings may assist in identifying gaps and priorities for researchers, clinicians, and policy makers and may inform the development of future trials that guide in- and out-of-hospital cardiac arrest care.

AUTHOR CONTRIBUTIONS

Conceptualization, methodology, data curation, investigation, formal analysis, project administration, visualization, writing—original draft, and writing—review and editing: Jake Toy. *Methodology, data curation, investigation, and writing—review and editing*: Lauren Friend, Kelsey Wilhelm, Michael Kim, and Claire Gahm. *Methodology, writing—review and editing, and supervision*: Ashish R. Panchal, David Dillon, Joelle Donofrio, Juan Carlos Montroy, Nichole Bosson, Ryan Coute, and Shira Schlesinger. *Conceptualization, methodology, writing—review and editing, and supervision*: Marianne Gausche-Hill. *Conceptualization, methodology, investigation, writing—review and editing, and supervision*: James Menegazzi.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Toy J, Friend L, Wilhelm K, et al. Evaluating the current breadth of randomized control trials on cardiac arrest: A scoping review. *JACEP Open*. 2024;5:e13334. https://doi.org/10.1002/emp2.13334