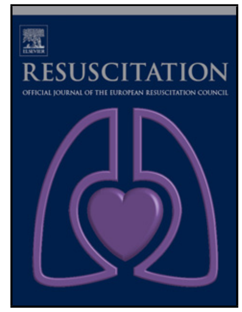
Accepted Manuscript



Title: Does care at a cardiac arrest centre improve outcome after out-of-hospital cardiac arrest? – A systematic review

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PII: S0300-9572(19)30029-2
DOI: https://doi.org/10.1016/j.resuscitation.2019.02.006
Reference: RESUS 7893

To appear in: *Resuscitation*

Received date: 15 December 2018
Revised date: 8 February 2019
Accepted date: 11 February 2019

Does care at a cardiac arrest centre improve outcome after out-of-hospital cardiac arrest? – A systematic review

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AIM

To perform a systematic review to answer 'In adults with attempted resuscitation after non-traumatic cardiac arrest does care at a specialised cardiac arrest centre (CAC) compared to care in a healthcare facility not designated as a specialised cardiac arrest centre improve patient outcomes?'

METHODS

The PRISMA guidelines were followed. We searched bibliographic databases (Embase, MEDLINE and the Cochrane Library (CENTRAL)) from inception to 1st August 2018. Randomised controlled trials (RCTs) and non-randomised studies were eligible for inclusion. Two reviewers independently scrutinized studies for relevance, extracted data and assessed quality of studies. Risk of bias of studies and quality of evidence were assessed using ROBINS-I tool and GRADEpro respectively. Primary outcomes were survival to 30 days with favourable neurological outcomes and survival to hospital discharge with favourable neurological outcomes. Secondary outcomes were survival to 30 days, survival to hospital discharge and return of spontaneous circulation (ROSC) post-hospital arrival for patients with ongoing resuscitation. This systematic review was registered in PROSPERO (CRD 42018093369)

RESULTS

We included data from 17 observational studies on out-of-hospital cardiac arrest (OHCA) patients in meta-analyses. Overall, the certainty of evidence was very low. Pooling data from only adjusted analyses, care at CAC was not associated with increased likelihood of survival to 30 days with favourable neurological outcome (OR 2.92, 95%CI 0.68 to 12.48) and survival to 30 days (OR 2.14, 95%CI 0.73 to 6.29) compared to care at other hospitals. Whereas patients cared for at CACs had improved survival to hospital discharge with favourable neurological outcomes (OR 2.22, 95%CI 1.74 to 2.84) and survival to hospital discharge (OR 1.85, 95%CI 1.46 to 2.34).

CONCLUSIONS

Very low certainty of evidence suggests that post-cardiac arrest care at CACs is associated with improved outcomes at hospital discharge. There remains a need for high quality data to fully elucidate the impact of CACs.

INTRODUCTION

There is wide variability in survival among hospitals caring for patients after resuscitation from out of hospital cardiac arrest (OHCA). OHCA is common, yet survival outcomes are poor, with substantial regional and international variation.[1-5] Survival from OHCA ranges from 8-16.1%. [6] Measures to maximise favourable neurological outcomes are a research priority for both patients and clinicians.[7] Post-resuscitation care, including percutaneous coronary intervention (PCI) and targeted temperature measurement (TTM), is an important component to achieve good neurological outcome. [8, 9]

In most countries, post resuscitation care is not regionalized to specialised hospitals. [10] There is wide variation among hospitals in the availability and type of post resuscitation care, as well as clinical outcomes. [11, 12] Patients with other time-sensitive emergencies (e.g. trauma, acute myocardial infarction and stroke services) are often triaged to centres which offer speciality services and greater provider experience. [13-16] Such centralised specialist services may improve the provision of targeted post-resuscitation care and offer similar benefits and improve patient outcomes after cardiac arrest.

The International Liaison Committee on Resuscitation (ILCOR) last considered the evidence on this topic in 2015 and concluded that specialist cardiac arrest centres (CACs) may be effective despite a lack of high quality data to support their implementation.[17] Previous observational studies have reported an association between transport to CAC and survival to hospital discharge, but there is inconsistency in the hospital factors that are related to optimal patient outcomes. Whilst most experts agree that a CAC should include a 24-hour cardiac catheterisation laboratory, targeted temperature management, and neurological services that offer electrophysiological modalities for monitoring and prognostication, discrepancies remain in the definition of services that constitute a specialist CAC.[18] The objective of this systematic review was to evaluate outcomes of adults with attempted OHCA resuscitation after care in a specialized cardiac arrest centre compared with care in an institute not designated as a specialized cardiac arrest centre.

METHODS

The protocol for this systematic review was registered with PROSPERO (CRD 42018093369) on 12th April 2018. Reporting of the systematic review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [19] The review was commissioned by ILCOR.

Search strategy and selection criteria

Bibliographic databases (Embase, MEDLINE and the Cochrane Library (CENTRAL)) were searched from inception to February 2018 using a combination of index terms and key words relating to the population, intervention and comparator. The search strategy was developed in conjunction with information specialists at St Michael's Hospital Health Sciences Library (see Supplementary Materials Appendix A for sample search strategy). Reference lists of relevant articles were checked, and clinical trial registers (www.clinicaltrials.gov, www.isrctn.com and http://www.who.int/ictrp/en/) were searched to identify on-going trials. (Supplementary Materials Appendix B) Endnote 8 (Thomson Reuters) was used to store records and facilitate screening. The search was repeated on 1st August 2018 to identify any additional studies published during the review process.

Study selection

Studies were eligible for inclusion if they met the following pre-defined criteria:

1) ***Population:*** Adults with attempted resuscitation after non-traumatic in-hospital or out-of-hospital cardiac arrest.

2) ***Intervention and Comparator:*** Care at a specialised cardiac arrest centre compared with care in a healthcare facility not designated as a specialised cardiac arrest centre

3) ***Outcomes:*** Primary outcomes were: survival at 30 days with favourable neurological outcome (defined as Cerebral Performance Category (CPC) 1 or 2, modified Rankin Scale (mRS) 0-3); and survival at hospital discharge with favourable neurological outcome (defined as CPC 1 or 2, mRS 0-3).[20, 21] Secondary outcomes were: survival at 30 days; survival at hospital discharge and return of spontaneous circulation (ROSC) after hospital admission.

4) ***Study Designs:*** Randomised controlled trials (RCTs) and non-randomised studies (non-randomised controlled trials, interrupted time series, controlled before-and-after studies, cohort studies) were eligible for inclusion. Unpublished studies (e.g., conference abstracts, trial protocols) were excluded. Studies reporting paediatric cardiac arrests (≤18 years old) and cardiac arrest secondary to trauma were excluded.

5) Timeframe: All years and all languages were included as long as there was an English abstract.

Studies were selected by two reviewers (JY/TM) independently by title screening and abstract. Full text of selected studies were retrieved and reviewed by two reviewers (JY/TM) independently. Reasons for exclusion were documented. Reference lists of included studies were also screened.

Definition of Cardiac Arrest Centre

Previous literature has described CACs as institutions that have access to a 24-hour cardiac catheterisation laboratory, targeted temperature management in a critical care facility and prognostication using multimodal approach including delayed clinical examination, neuroelectrophysiological measurements and biomarkers.[22] As there is no widely accepted definition of a cardiac arrest center, we expected variation in description of healthcare institutions and terminology.[18] We accepted ‘cardiac arrest centre’ or ‘regionalized cardiac arrest care’ or ‘high case volume centres’ of similar description in the literature.

Data Extraction and Quality Assessment

A piloted and standardised data extraction form was used to record information on study design, patient population and characteristics, sample size, description of CAC, and outcomes. Two reviewers independently (JY/TM) conducted data extraction (study design, study population, outcome measures and study quality). Any disagreement surrounding the selection of a manuscript or data extraction were resolved either by consensus or arbitration by a third reviewer (MS). Two reviewers (JY/TM) assessed risk of bias of individual studies independently, using the Cochrane Collaboration risk of bias tool[23] for randomised controlled trials and the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I tool)[24] for non-randomised studies. Disagreements were resolved by discussion between the two reviewers.

Data analysis and synthesis

We used meta-analyses to synthesise evidence by outcome, where this approach was not precluded. Generic inverse variance method and random-effects model were used to compute the odds ratio (OR) and 95% confidence interval for dichotomous outcomes.[25] We measured statistical heterogeneity using the Higgins I^2 statistic.[26] We contacted study authors for additional data when it was directly relevant to our outcomes of interest. For observational studies where more than one type of analysis was reported, we preferentially used adjusted or matched case analyses, over unadjusted analyses in meta-analyses. Due to perceived substantial clinical heterogeneity, only effect estimates from adjusted analyses were pooled. In addition, the decision was to pool outcomes only if the effects were in the same direction.

We planned *a priori* subgroup analyses comparing outcomes from patients with shockable and non-shockable initial cardiac rhythm; and direct transfer versus secondary transfer to CACs. In addition, we undertook additional sensitivity analyses to test the robustness of our findings. Firstly, we assessed the impact of our hierarchical approach to selection of analysis type in observational studies by testing the use of other analyses on overall findings. Secondly, we attempted to identify the source of heterogeneity by performing *post-hoc* sensitivity analyses of studies that only included patients with prehospital ROSC and also studies with before-and-after study designs.

The certainty of evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) system in GRADEpro Guideline Development Tool (Evidence Prime, Inc., McMaster University).[27, 28] Review Manager version 5.3 (The Cochrane Collaboration, 2014) was used to produce forest plots.[29]

RESULTS

After removal of duplicates, the literature search yielded 3,065 unique references (3061 from original search and 4 additional studies from updated search). After screening, 22 studies (one randomised controlled trial [30], one prospective study, 4 before and after studies and 16 retrospective analyses) fulfilled eligibility criteria and were included in qualitative synthesis. (Figure 1) Studies were conducted in Australia (n=3), North America (n=8), Europe (n-7) and South East Asia (n=4). The kappa value for identifying studies during initial screening was 0.83. Table 1 contains characteristics of included studies.

Data from 22 OHCA studies were included in the qualitative synthesis, with data from 17 observational studies included in meta-analysis. We described but did not include 5 studies in the meta-analysis: one randomised study since it presented only pilot feasibility data (33 patients, main trial is on-going) [30], three observational studies that only included patients who were discharged alive from hospital and reported long-term outcome data [31-33], and one study which examined the impact of a Post Arrest Consult Team on post cardiac arrest care processes and outcomes.[34]

We found no studies reporting data for in-hospital cardiac arrest patients. One study included in-hospital and out-of-hospital cardiac arrest patients but outcomes were not reported separately.[32]

Risk of bias for individual studies

One randomised controlled study reporting pilot outcomes had moderate overall risk of bias due to lack of treatment allocation. (Table 2a) Twenty-one observational studies had either moderate (n=9) or serious (n=12) overall risk of bias. The most common sources of bias were inadequate adjustment of confounding factors, subject selection (e.g. only including survivors), outcome measurement, and missing data. There was little to no bias from result reporting or the classification of and deviation from the intervention. (Table 2b)

Certainty of evidence across studies

The overall certainty of evidence was very low across all outcomes, primarily due to risk of bias and inconsistency. GRADE summary tables are provided in Appendix C (Supplementary Materials).

Primary outcomes

Survival at 30 days with favourable neurological outcomes (critical)

Survival to 30 days with favourable neurological outcomes were reported by three studies (one retrospective cohort study and one before and after study with adjusted analyses, and one before and after study with unadjusted analyses) recruiting 46,164 patients. [35-37] (Figure 2) In pooled data from two studies (n=45,956) care at CACs was not associated with increased likelihood of a favourable neurological outcomes at 30 days compared to other hospitals (OR 2.92, 95% CI 0.68 to 12.48). There was moderate to substantial heterogeneity (I^2 73%) and certainty of evidence was very low. One study reporting unadjusted data, also found no association.[37]

Survival at hospital discharge with favourable neurological outcomes (critical)

Survival to hospital discharge with favourable neurologic outcome was reported by six studies. Four studies was included in meta-analysis (one retrospective cohort study and one before and after study with adjusted analyses, and two retrospective cohort studies with unadjusted analyses) recruiting a total of 30,080 patients were included in meta-analysis. [30-33] In pooled data from two studies (n=3,673), care at a CAC was associated with increased likelihood of surviving to hospital discharge with favourable neurological outcome compared to other hospitals (OR 2.22 95% CI 1.74 to 2.84). (Figure 3) There was no statistical heterogeneity (I^2 0%) and certainly of evidence was assessed as very low. The direction of effect in two studies reporting unadjusted data favoured care at CACs but was no longer significantly after adjusted analyses. [38, 39] Two studies using an indirect measure (discharge destination) also favoured care at CACs for this outcome. [40, 41]

Secondary outcomes

Survival to 30 days (critical)

Survival to 30 days was reported in six studies (two retrospective cohort studies with adjusted analyses, one before and after study and three retrospective cohort studies with unadjusted analyses) recruiting a total of 45,066 patients. [33, 35, 37, 42-44] In pooled data from two studies (n=2,693) care at a CAC was associated with increased likelihood of survival to 30 days post admission (OR 2.14 95% CI 0.73 to 6.29). (Figure 4) There was considerable statistical heterogeneity (I^2 86%) and the certainty of evidence was assessed to be very low. Three of the four studies reporting unadjusted data for this outcome report favourable survival for patients admitted to CACs.

Three additional studies examined long-term survival of cardiac arrest patients by focusing explicitly on the outcomes of patients discharged alive from hospital, these were not included in the meta-analysis. All three studies found that CAC admission was associated with better patient survival. [28-30].

Survival to hospital discharge (critical)

Survival to hospital discharge was reported in ten studies (three retrospective cohort studies and two before and after studies with adjusted analyses, and five retrospective analyses with unadjusted analyses) including 42780 patients. [38-40, 45-50] Data from meta-analysis of 5 studies (n=11,662) found care at a CAC was associated with increased likelihood of survival to hospital discharge compared to other hospitals (OR 1.85 95% CI 1.46 to 2.34). (Figure 5) There was moderate statistical heterogeneity (I^2 69%) and certainty of evidence was assessed to be very low. All five studies reporting unadjusted support the association of the pooled analysis.

Return of spontaneous circulation (ROSC) post hospital admission for patients with ongoing CPR (important)

Data on ROSC post hospital admission for patients with ongoing CPR was obtained from authors of two studies (one retrospective cohort study and one before and after study with unadjusted analyses) comprising which reported post hospital admission ROSC rates in patients with ongoing CPR. [35, 36] (Figure 6) Both studies reported significantly higher ROSC rates in CAC group but data was not pooled based on the lack of adjusted data.

Subgroup Analyses and sensitivity analyses

There were insufficient data to perform the pre-planned pooled subgroup analyses of subjects with shockable vs. non-shockable initial cardiac rhythm, and direct transfer vs. secondary transfer to CAC.

Eight studies [33, 36, 37, 45, 48-51] reported outcomes in CAC versus non-CACs stratified by shockable or non-shockable rhythms. Data were too heterogeneous to allow for meta-analysis (Supplementary Materials Table 3). In patients with shockable rhythm, four studies reported improved outcomes at CACs [36, 48, 49, 51], and three studies reported no difference [37, 45, 50]. In patients with non-shockable initial rhythms, CACs were associated with improved outcomes in one study [51] and no difference in two studies [49, 50].

The majority of the included studies compared OHCA patients who were directly transport to a CAC to those transported to a non-CAC. Only three studies examined outcomes in OHCA patients who were transferred to a CAC from a non-CAC [33, 36, 41]. In these studies, the proportion of patients with secondary transfers were small and, although two studies [33, 41] adjusted for available confounders, there is potential for referral bias (whereby the sickest or those most likely to survive were transferred to CACs). A US study [33] reported no difference in long-term survival between primary and secondary transfers to CACs after adjusting for potential confounders (or in unadjusted 30-day survival data provided by the authors). After conducting numerous analyses to adjust for referral bias, but the study consistently reported increased long-term survival in patients cared for at CACs, with the lowest mortality seen in early transfers. An Australian study [41] reported higher (adjusted) survival in patients who were transferred directly to a CAC compared to secondary transfers. A small subgroup analysis by Tagami [36] found no difference in survival to 30-days with favourable neurological outcome in patients between direct and secondary transfer to CACs.

Sensitivity analysis replacing adjusted analyses with unadjusted analyses were performed for the outcomes of survival to 30 days with favourable neurological outcomes, survival to hospital discharge with favourable neurological outcomes, survival to 30 days and survival to hospital discharge. These replacements made no difference to our overall findings (data not shown). We performed sensitivity analyses to explore the source of heterogeneity by firstly excluding data from studies that transported only patients with pre-hospital ROSC [38, 40, 45, 46] for two outcomes: Survival to hospital discharge with favourable outcomes (2 studies) and Survival to hospital discharge (4 studies). This did not change our overall findings but did reduce statistical heterogeneity in Survival to hospital discharge from I^2 90% to 52% (data not shown). Secondly, we performed sensitivity analyses by excluding studies of before and after design [36, 37, 48, 49] for three outcomes: Survival to hospital discharge with favourable outcome (1 study), Survival to 30 days (1 study), and Survival to hospital discharge (2 studies). The results were again similar to our main analyses (data not shown).

DISCUSSION

This is the most comprehensive and up to date systematic review and meta-analysis examining the impact of care at CACs compared with other hospitals on patient outcomes from OHCA. This review included data from large registries contributed by different countries. Patients cared for at CACs had increased likelihood of survival to hospital discharge and survival to hospital discharge with favourable neurological outcomes. However, there was no evidence that care at CACs improve survival to 30 days and survival to 30 days with favourable neurological outcomes. For patients with on-going CPR, care at CACs did not improve post-hospital arrival ROSC compared with other hospitals but this may be due to limited study size.

Whilst our findings are generally supportive of transporting OHCA patients to CACs, they should be interpreted with caution. Pooled data were extracted from retrospective and before-after studies, which all suffered from moderate or serious risk of bias. Study data was collected from different countries each with their distinctive healthcare systems and unique differences in system design, clinical practice, resuscitation and transporting policy of emergency medical services. Whilst some studies presented adjusted data and multivariate analyses, it may not be possible to adjust for unknown or unanticipated confounding factors, thereby limiting the internal validity of source evidence. The overall certainty of evidence was very low, preventing us from making firm conclusions based on our findings. In addition, most studies conducted thus far have focused on care at a CAC per se, rather than on the more important question of whether patients that have an OHCA close to a non-CAC should be redirected for direct transportation to a CAC. Such studies conducted in different settings should include a more detailed analysis on possible problems associated with longer transportation times.

Relevant issues include the safety and logistics of longer prehospital transport time, the risk of re-arrest and other adverse events, the negative impact of transport on CPR quality, and whether to bypass a local hospital or arrange for secondary transfer after stabilization at a local hospital. [52-54] Our review did not specifically investigate the impact of transport duration on patient outcomes but did include some studies that reported transport times. Using a mathematical model, Kragholm, et al. concluded that there is survival benefit for cardiac arrest patients with prehospital ROSC to be transported to CAC even if journey time exceeds 20 minutes. [46] Similar findings were reported by Tranberg et al. who also reported that distances from arrest location to CAC was not associated with patient survival. [43] In contrast, regression analyses from Cournoyer study stated that increasing the delay from call to hospital arrival by 14.0 min would offset the potential survival benefit of being transported to a PCI-capable centre.[50] The decision whether to transport a patient and the hospital destination are likely to differ in urban, suburban, and rural settings. [55] Appropriately validated decision-making and risk prediction tools may help guide rescuers with transport and treatment decisions in future studies. [56, 57] Future clinical trials should also include the critical outcome of long term survival with favourable neurological outcomes to address this research gap.[7]

There was only one pilot randomised controlled study which reported only feasibility outcomes and did not demonstrate a difference between 30-day survival (CAC 9/18 50% vs other 6/15 40%) or 30-day survival with favourable neurological outcome (CAC 9/18 50% vs other 7/14 50%). [30] This study has just started recruiting. High quality evidence is needed to test the impact of CAC post cardiac arrest care on patient outcomes and address several remaining clinical knowledge gaps. For instance, specific subgroups of subjects (e.g. cardiac aetiology, shockable initial cardiac rhythm, ROSC or no ROSC prior to hospital admission) may benefit more or less from regional CAC care.

A key limitation is the general lack of consensus on what constitutes a CAC. In light of this, we accepted the study authors' definitions and descriptions of regional hospitals with a large case volume and coronary intervention capacity as a CAC. Likewise, we have not been able to substantiate or disprove these stated levels of service or other touted elements of post arrest care. We urge the Utstein writing group to consider CAC definition in the next iteration of Utstein variables for OHCA. Whilst clinical expertise and post arrest intervention should be readily available in CAC, hospital admission does not necessarily mean that patients receive all elements of post arrest care. Patient care may be affected by other healthcare system pressures such as lack of resources or availability. Further considerations should also be given to hospital characteristics such as the number of cardiac arrest cases and other post-resuscitation hospital processes.[34, 58-61] A substantial challenge remains in identifying those components of post cardiac arrest care provided by a CAC that improve patient outcomes, especially recognizing the spectrum of disease severity across the post cardiac arrest syndrome and potential for tailored bundles of care.

From the included studies, the volume and annual case load of cardiac arrest did not improve patient survival in either CAC or other hospital setting. Mumma, et al. examined patient survival and neurological outcomes in CACs with different annual volume of cases (≤40 cases/year vs ≥40 cases/year) and found both survival and neurological outcomes of cardiac arrest patients were higher in CACs regardless of volume status.[51] There was also no reported difference in outcomes by hospital volume status (2 studies in CAC [40, 45], 1 study other hospitals [35], 1 study across all hospitals[38]).

Additional logistical and organization knowledge gaps remain in post cardiac arrest care. Regionalised post-cardiac arrest care is not feasible without a robust supporting network and regionalisation of medical services at the local and municipal levels.[62, 63] Fortunately, the trauma, STEMI, and stroke systems of care provide a template to establish a similar infrastructure for cardiac arrest. The success of whole system change such as those seen in major trauma systems cannot be ignored, and it needs to be highlighted that this change was not based on data from high quality randomized controlled trials but on observational data.[64] CAC services could potentially overlap with the cardiovascular and neurologic services offered at regional STEMI and stroke centres. Whilst indirect evidence established the cost effectiveness of stroke and STEMI centres, [65, 66] the cost effectiveness of specific strategies focusing on cardiac arrest patients and their potential impact on the care of other patient groups remains unknown.

The studies included in our review focused on clinical outcomes such as survival that has traditional been considered to be of critical importance. Through the work of Core Outcome Set for Cardiac Arrest, there is a clear need for future research to address outcomes that are relevant and important to patient and their family such as quality of life and organ donation. [7, 67]

Limitations

We encountered high statistical heterogeneity in our meta-analysis and scrutinised included study characteristics for potential source of bias. Four studies [38, 40, 45, 46] included only patients with prehospital ROSC in their analysis, possibly due to local policy and clinical practice.[68, 69] Survival from patients with no pre-hospital ROSC and requiring ongoing CPR may be better than commonly believed.[70] Before-and-after study designs used in four studies [36, 37, 48, 49] may not adequately control for changes in clinical practice. Both sets of sensitivity analyses did not adequately explain statistical heterogeneity. There was insufficient data from included studies for us to examine specifically whether there is any difference in outcomes for patients who present with shockable vs. non-shockable initial cardiac rhythm. We were also unable to conclusively assess the impact of direct transfer vs. secondary transfer to CAC. There was also no meaningful data to examine whether care at CAC has any influence on patient outcomes from in-hospital cardiac arrest compared to other hospitals.

CONCLUSIONS

Very low certainty evidence suggests that post-cardiac arrest care at cardiac arrest centres is associated with improved survival with favourable neurological outcome at hospital discharge and improved survival to hospital discharge. Care at CACs did not improve survival to 30 days with favourable neurological outcome and survival to 30 days. There remains a need of high quality data individual patient data meta-analysis and or data from randomised trials to fully elucidate the impact of CAC.

CONFLICTS OF INTEREST

Joyce Yeung was compensated by ILCOR for her work related to this review. TM and JB were authors of two studies included in this review. The other authors declare no competing conflict of interests.

ACKNOWLEDGMENTS

This Systematic Review was funded by the American Heart Association, on behalf of The International Liaison Committee on Resuscitation (ILCOR) for manuscript submission to the editor. The following authors received payment from this funding source to complete this systematic review:

Joyce Yeung as Expert Systematic Reviewer.

Nazi Torabi and Glyneva Bradley-Ridout as Information Services, St Michael’s Hospital.

JY is supported by National Institute of Health Research Post-Doctoral Fellowship. JB is funded by a Heart Foundation Fellowship (#101171)

The authors would also like to acknowledge the contribution of Dr Eunice Singletary (ILCOR Continuous Evidence Evaluation liaison), Dr Robert Grief, Dr Farhan Bhanji (Education, Implementation and Team Task Force co-chairs) and Education, Implementation and Team Task Force and Advanced Life Support Task Force members.

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TM and JB were authors of two studies included in this review. Markus Skrifvars has received lecture fees from BARD MEDICAL and a research grant from GE Healthcare and INVOS COVIDIEN. The other authors declare no competing conflict of interests.

FUNDING ACKNOWLEDGMENT

This Systematic Review was funded by the American Heart Association, on behalf of The International Liaison Committee on Resuscitation (ILCOR). The following authors received payment from this funding source to complete this systematic review: Joyce Young as Expert Systematic Reviewer, Nazi Torabi and Glyneva Bradley-Ridout at Information Services, St Michael's Hospital.

ACKNOWLEDGEMENTS

JY is supported by National Institute of Health Research Post-Doctoral Fellowship. JB is funded by a Heart Foundation Fellowship (#101171).

The authors would also like to acknowledge the contribution of Dr Eunice Singletary (ILCOR Continuous Evidence Evaluation liaison), Dr Robert Grief, Dr Farhan Bhanji (Education, Implementation and Team Task Force co-chairs) and Education, Implementation and Team Task Force and Advanced Life Support Task Force members.

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LEGENDS TO FIGURES

Figure 1 PRISMA Diagram

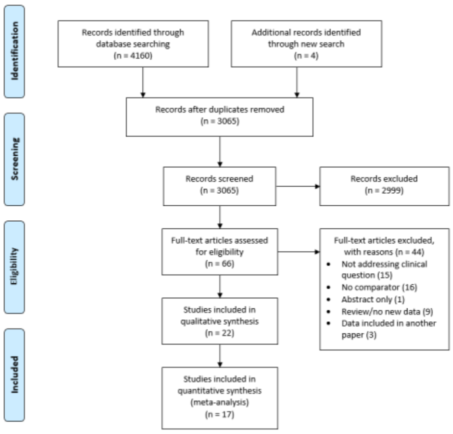

Figure 2 Survival to 30 days with favourable outcome. Higher Odds Ratio favours CAC.

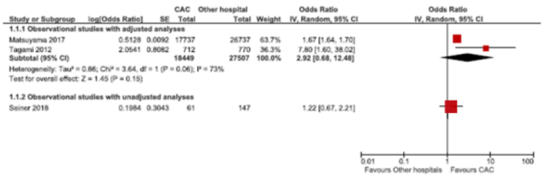

Figure 3 Survival to hospital discharge with favourable outcome. Higher Odds Ratio favours CAC.

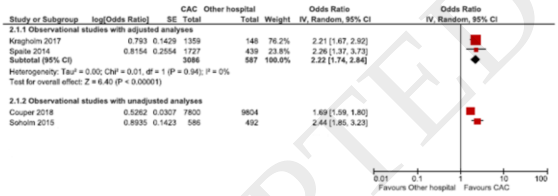

Figure 4 Survival to 30 days. Higher Odds Ratio favours CAC.

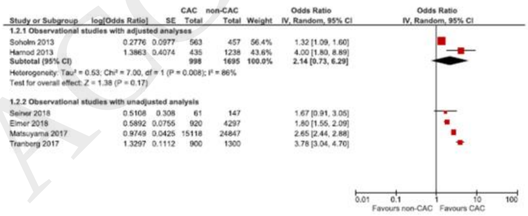

Figure 5 Survival to hospital discharge. Higher Odds Ratio favours CAC.

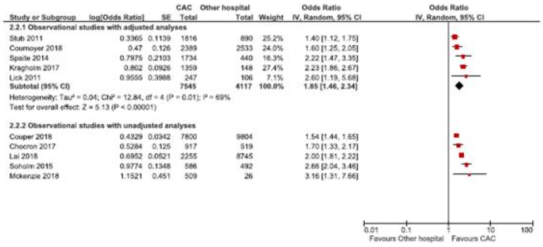

Figure 6 Return of spontaneous circulation post-hospital arrival in patients with ongoing resuscitation. Higher Odds Ratio favours CAC.

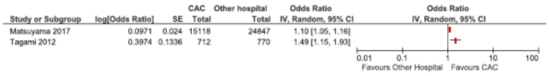

Table 1 Characteristics of included studies

Study	Setting	Study Design	Sample size	Population	Description of CAC	Key relevant findings
Andrew 2017*[#]	Victoria, Australia	Retrospective cohort using registry data 2000-2014 Victoria Ambulance Cardiac Arrest registry	Total 3449 CAC 2775 nonCAC 674	All OHCA survivors to hospital discharge	PCI capable hospital	• Care at CAC was associated with long term survival post hospital discharge in multivariate analyses
Brooks 2016*[#]	Canada	Prospective cohort study 2011-2013	Total 1006 CAC (2 hospitals with Post Arrest Consult Team, PACT) 151 nonCAC (no PACT) 855	Non traumatic OHCA, aged >18, GCS<10 on ED arrival, survive for 6hrs	Post arrest consult team (PACT) On call doctor and nurse 24/7, review every 24hrs Advice on TTM, PCI, electrophysiology assessment, neuroprognostication	• PACT hospital was not associated with survival to hospital discharge or survival with good neurologic status (mRS 0-2) in adjusted analyses
Chocron 2017	Paris, France	Retrospective analysis from database Paris Sudden Death Expertise Centre 2011-2013	Total 1436 CAC 917 nonCAC 519	Non traumatic >18, OHCA achieved ROSC, admitted alive	High case volume with PCI 24/7	• Care at CAC was associated with survival to discharge in univariate analysis but not in multivariate analyses
Couper 2018	United Kingdom	Retrospective analysis using Myocardial Ischaemia National Audit Project Database	Total 17604 PCI centres 7800 nonPCI centres 9804	Aged >18, OHCA, achieved ROSC prehospital care	PCI centres performing >100 cases/year	• Care at CAC was associated with survival to discharge in univariate analysis but not in multivariate analyses
Cournoyer 2018	Montreal, Canada	Retrospective cohort study using a registry of OHCA from the region of Montreal, Canada April 2010 until December 2015	Total 4922 CAC 2389 nonCAC 2533	Aged >18, All transported non-traumatic OHCA without 'do-not-resuscitate' directives or with 'obviously deceased' criteria	PCI-capable hospital (STEMI centre) with PCI or hemodynamic support 24/7	• Care at CAC was associated with survival to discharge in adjusted analyses
Elmer 2016*[#]	Southwestern Pennsylvania, USA	Retrospective analysis from database 2005-2013 IHCA and OHCA	Total 987 CAC (1 CAC) 680 nonCAC (2 moderate volume tertiary centres 4 low volume centres) 307	Aged>18, IHCA and OHCA who survived to discharge (exclude trauma, neurological catastrophe)	Regional referral centre organised post arrest care	• Care at high volume CAC was associated with survival to hospital discharge with good neurological outcome in adjusted analyses
Elmer 2018[#]	Southwestern Pennsylvania, USA	Retrospective analysis from EMS database 2010-2014 OHCA	Total 5217 CAC 920 nonCAC 4297 • Direct 570 • Secondary 350	Aged>16yrs, OHCA with prehospital ROSC, including secondary transfer	'Cardiac arrest receiving centre' – receiving at least 1 interfacility transfer OHCA patient every 3 months	• Care at CAC was associated with long term survival in adjusted analyses

Harnod 2013	Taiwan	Retrospective cohort using National Health Insurance Research database 2005-2007	Total 1673 CAC (22 medical centres) 435 nonCAC (72 Regional hospitals, 367 district hospitals) 1238	Aged >15yrs, OHCA (exclude Trauma, without intubation or CPR in ED)	'Medical centres'	• Care at CAC was associated with survival at 30 days after hospital discharge in adjusted analyses
Kragholm 2017	USA Cardiac Arrest Registry to Enhance Survival (CARES)	Retrospective analysis from CARES database 2012-2014	Total 3449 CAC 1359 nonCAC 148	Arrests of presumed cardiac cause with prehospital ROSC	PCI centre (primary PCI was available on a 24/7 basis)	• Care at CAC was associated with improved survival to hospital discharge with good neurological outcome and survival to hospital discharge in adjusted analyses
Lai 2018	Taiwan	Retrospective cohort using National Health Insurance Research database 2007 to 2013	Total 11000 CAC 2255 nonCAC 8745	OHCA with codes of VF and cardiac arrest (exclude <18, Unknown outcomes, trauma)	Medical centres	• Care at CAC is associated with survival to hospital discharge in adjusted analyses
Lick 2011	Minnesota, USA	Before and after (2005 compared with 2006-2007)	Total 353 CAC 247 nonCAC 106	All OHCA	Take Heart Program Cardiac arrest centres/Resuscitation centre of excellence: TTM, 24/7 PCI, electrophysiology, outcome tracking	• Care at CAC was associated with survival to hospital discharge in adjusted analyses • Care at CAC was not associated with improved mean CPC score at discharge in adjusted analyses
Matsuyama 2017[#]	Osaka, Japan	Retrospective analysis Utstein Osaka Project 2005-2012	Total 44,474 CAC (16CCMC) 17,737 nonCAC (301 non-CCMC) 26,737	Aged >18, OHCA , resuscitated by EMS and brought to hospital, all causes	Critical care medical centre: ≥20 beds and ICU for critically ill patients, capable of ECPR or PCI and TTM 24/7.	• Care at CAC was associated with survival at 30 days with good neurological outcome, survival at 30 days and ROSC in adjusted analysese
McKenzie 2018	Perth, Australia	Retrospective analysis St John Ambulance Western Australia OHCA Database January 2012 to December 2015	Total 539 Non CAC 26 CAC 513 • Direct 408 • Secondary 105	Aged >18, OHCA, admitted to and survived ED care	24/7 PCI centre and post resuscitation care	• Care at CAC was associated with survival to hospital discharge in adjusted analyses • Direct transport to CAC was associated with survival to hospital discharge in adjusted analyses • Indirect transport to CAC was associated with increased risk of death up to 12-months in adjusted analyses
Mumma 2015	California, USA	Retrospective cohort using registry data 2011	Total 7725 CAC (125 STEMI centre) 5202 nonCAC (208 non-STEMI centre) 2523	Discharge database with cardiac arrest on care	STEMI centre: 24/7 PCI and TTM, >40 patients/yr ROSC post OHCA	• Care at CAC was associated with survival at hospital discharge with good neurological outcome (defined as discharge to home, residential care facility, prison, jail, another hospital for

						nonacute care, left against advice) in adjusted analyses
Patterson 2017*	London, UK	Pilot study of Randomised controlled trial	Total 33 CAC (one hospital) 18 nonCAC (6 hospitals) 15	Aged >18, OHCA , witnessed VF presumed cardiac cause, attended by advanced paramedic practitioners	24/7 PCI,GDT, TTM	• Care at CAC was not associated with survival at 30 days with good neurological outcome, survival at 30 days in adjusted analyses (pilot outcome only)
Seiner 2018	Liberec, Czech	Before and after study 2013-2015 compared to 2016-2017	Total 33 CAC (After) 61 nonCAC (Before) 47	Aged >18, OHCA , all cause	Cardiovascular centre with 24/7 cath lab, PCAS	• Care at CAC was not associated with survival at 30 days with good neurological outcome and survival at 30 days in unadjusted analyses
Soholm 2013	Copenhagen, Denmark	Retrospective registry 2002-2010	Total 1020 CAC 563 nonCAC 457	OHCA with or without ROSC, dispatch of paramedic & anaesthetist include non-cardiac Excludes STEMI	Tertiary hospital 24/7 cath lab, cardiac ITU, TTM (from 2004)	• Care at CAC was associated with survival to 30 days in adjusted analyses
Soholm 2015	Copenhagen, Denmark	Retrospective analysis 2002-2011	Total 33 CAC (2 tertiary university heart centres) 586 nonCAC (6 non-tertiary university hospital) 492	Aged >18, OHCA transported with ROSC or ongoing CPR Excludes STEMI	Tertiary centre: heart centre with dedicated anaesthetists, cardiologists and surgeons. Interventional cardiology and cardiac surgery 24/7, cardiac ICU, TTM (2002-2004)	• Care at CAC was associated with survival to hospital discharge and survival at 30 days in adjusted analyses • Care at CAC was not associated with survival to hospital discharge with good neurological outcome in adjusted analyses
Spaite 2014	Arizona, USA	Before and after 2007-2010 After: (December 14, 2007, to November 25, 2010) Before: (January 1, 2007, and December 13, 2007)	Total 2177 CAC 1737 nonCAC 440	Aged >18, OHCA presumed cardiac transported	Cardiac receiving centre Coronary angiography/PCI, TTM, Statewide regionalisation	• Care at CAC was associated with survival to hospital discharge and surivival to hospital discharge with favourable neurological outcomes in adjusted analyses
Stub 2011	Victoria, Australia	Retrospective analysis 2003-2010 Victoria ambulance data	Total 2706 CAC 1816 nonCAC 890	Aged>18, OHCA presumed cardiac transported with ROSC	24hr cardiac interventional service	• Care at CAC was associated with survival to hospital discharge in adjusted analyses • Care at CAC was associated with survival to hospital discharge with favourable neurological outcome (defined as discharge home) in unadjusted analyses

Tagami 2012	Aizu, Japan	Before and after 2006-2008 compared with 2009-2010	Total 1482 CAC 712 nonCAC 770	OHCA transported with ROSC or ongoing CPR	Post resuscitation care centre: Tertiary centre PCAS, TTM, PCI	• Care at CAC was associated with survival at 30 days with good neurological outcome and survival to discharge in adjusted analyses
Tranberg 2017[#]	Denmark	Retrospective analysis 2001-2013 Danish Cardiac Arrest Registry	CAC 900 nonCAC 1300	All OHCA	High-volume invasive heart centres with a 24-h PCI service	• Care at CAC was associated with survival at 30 days in adjusted analyses

*Study data not included in meta-analysis; [#] Authors contacted to provide additional data

CAC: Cardiac arrest centre; nonCAC: other institution not designated as CAC; CPC: cerebral performance category; ECPR: extracorporeal CPR; ED: emergency department; GCS: Glasgow Coma Score; ICU: intensive care unit; IHCA: in-hospital cardiac arrest; OHCA: out-of-hospital cardiac arrest; PCAS: Post cardiac arrest service; PCI: Primary Coronary Intervention; QoL: Quality of life; ROSC: Return of spontaneous circulation STEMI: ST-elevation myocardial infarction; TTM: Targeted temperature management; VF: ventricular fibrillation

Table 2a Risk of bias – randomised study

Study	Randomisation (selection bias)	Allocation concealment (selection bias)	Performance and Detection bias	Attrition bias	Reporting bias	Other bias
Patterson 2017	LOW	HIGH	UNCLEAR	LOW	LOW	PILOT STUDY

Table 2b Risk of bias – non randomised studies

Study ID	Bias in confounding	Bias in patient selection	Bias in classification of intervention	Bias in deviation from intervention	Bias from missing data	Bias from measuring outcomes	Bias from selected reporting of results	Overall
Andrew 2017	Serious	Moderate	Low	Low	Moderate	Moderate	Low	Serious[a]
Brooks 2016	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Chocron 2017	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Couper 2018	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Cournoyer 2018	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Elmer 2016	Serious	Serious	Low	Moderate	Low	Moderate	Low	Serious[b]
Elmer 2018	Serious	Serious	Low	Low	Moderate	Moderate	Low	Serious[b]
Harnod 2013	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious[c]
Kragholm 2017	Serious	Moderate	Low	Low	Moderate	Moderate	Low	Serious[d]
Lai 2018	Serious	Serious	Low	Low	Low	Serious	Low	Serious[e]
Lick 2011	Serious	Serious	Low	Low	Low	Serious	Low	Serious[f]
Matsuyama 2017	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Mckenzie 2018	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Mumma 2015	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Seiner 2018	Serious	Low	Low	Low	Low	Moderate	Low	Serious[g]
Soholm 2013	Serious	Moderate	Low	Low	Moderate	Moderate	Low	Serious[h]
Soholm 2015	Serious	Serious	Low	Low	Low	Moderate	Moderate	Serious[i]
Spaite 2014	Serious	Moderate	Low	Low	Moderate	Moderate	Low	Serious[j]
Stub 2011	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Tagami 2012	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Tranberg 2017	Serious	Moderate	Low	Low	Moderate	Moderate	Low	Serious[k]

[a] only survivors were included

[b] only survivors were included, included interhospital transfer patients

[c] inadequate adjustment of confounding factors

[d] Difference in EMS response time, transfer times, whether bypass hospital, urban/rural arrest location

[e] only those with prehospital ROSC included which is dependent on transfer time and other confounders; coding does not differentiate between pre-existing conditions and secondary diagnoses

[f] a system of change including CPR training, bystander CPR, TTM, introduction of mechanical CPR device; differences in rate of patient recruitment before and after phase

[g] inadequate adjustment for confounders

[h] excluded all STEMI patients

[i] excluded all STEMI patients, included patients from 2013 paper

[j] included CPR training program, EMS transfer rates

[k] assumption of location of arrest in 23% of patients, significant temporal changes in bystander CPR rates