Review

Long-term neurologically intact survival after extracorporeal cardiopulmonary resuscitation for in-hospital or out-of-hospital cardiac arrest: A systematic review and meta-analysis

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Abstract

Background: Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) has been used as extracorporeal cardiopulmonary resuscitation (ECPR) to support further resuscitation efforts in patients with cardiac arrest, yet its clinical effectiveness remains uncertain.

Objectives: This study reviews the role of ECPR in contemporary resuscitation care compared to no ECPR and/or standard care, e.g. conventional CPR, and quantitatively summarize the rates of long-term neurologically intact survival after adult in-hospital cardiac arrest (IHCA) or out-of-hospital cardiac arrest (OHCA).

Methods: We searched the following databases on January 31st, 2020: CENTRAL, MEDLINE, Embase, and Web of Science. We followed PRISMA guidelines and used PICO format to summarize the research questions. Risk of bias was assessed using the ROBINS-I tool. Pooled risk ratios (RRs) for each outcome of interest were calculated. Quality of evidence was evaluated according to GRADE guidelines.

Results: Six cohort studies were included, totaling 1750 patients. Of these, 530 (30.3%) received the intervention, and 91 (17.2%) survived with long-term neurologically intact survival. ECPR compared to no ECPR is likely associated with improved long-term neurologically intact survival after cardiac arrest in any setting (risk ratio [RR] 3.11, 95% confidence interval [CI] 2.06−4.69; p < 0.00001) (GRADE: Very low quality). Similar results were found for long-term neurologically intact survival after IHCA (RR 3.21, 95% CI 1.74−5.94; p < 0.0002) (GRADE: Very low quality) and OHCA (RR 3.11, 95% CI 1.50−6.47; p < 0.002) (GRADE: Very low quality). Long-term time frames for neurologically intact survival (three months to two years) were combined into a single category, defined a priori as a Glasgow-Pittsburgh cerebral performance category (CPC) of 1 or 2.

Conclusions: VA-ECMO used as ECPR is likely associated with improved long-term neurologically intact survival after cardiac arrest. Future evidence from randomized trials is very likely to have an important impact on the estimated effect of this intervention and will further define optimal clinical practice. Review registration: PROSPERO CRD42020171945.

Keywords: ECPR, Extracorporeal cardiopulmonary resuscitation, Extracorporeal life support, Cardiac arrest

Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR), or cardiopulmonary resuscitation (CPR), assisted by veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a method of temporary mechanical circulatory support based on utilization of an extracorporeal membrane oxygenation (ECMO) system.[1−3] All VA-ECMO circuits consist of a venous cannula, usually placed in the right or left common femoral vein for extraction, while an arterial cannula is usually placed in the right or left femoral artery for infusion, and a membrane oxygenator where gas exchange occurs is connected to a centrifugal pump with a heat exchanger.[3−7]

Neither the guidelines of the American Heart Association (AHA) nor those of the European Resuscitation Council (ERC) recommend the routine use of ECPR for cardiac arrest (Class IIb, LOE C-LD).[8−11] However, ECMO-facilitated resuscitation has been increasingly used to assist early return of perfusion, supporting further resuscitation in order to mitigate the multi-organ dysfunction that accompanies in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA).[12−15] Currently, 129,037 patients are enrolled in the January 2020 Extracorporeal Life Support Organization (ELSO) Registry database, including 2387 adults with ECPR who survived to discharge (or transfer), with the number of cases in which VA-ECMO was used as ECPR increasing in the last decade. Overall survival to discharge/transfer after the use of ECPR for cardiac arrest was 29.0%.[12]

Outcomes of early deployment of VA-ECMO as ECPR for IHCA or OHCA in prior research have varied greatly among a range of study designs that include case series, case-control, and cohort studies. This approach has been associated with a 2- to 4-fold (8.0%−15.0% to 30.0%−45.0%) increase in patient-centered outcomes, including survival to discharge and neurologically intact survival.[16−54] An unexplored outcome of this approach is long-term neurologically intact survival in patients with cardiac arrest who respond poorly to the current standard of care.[45−50] Thus, identifying the rates of neurologically intact survival and optimal clinical practice in this patient population remains a high priority, as is the role of early ECMO-facilitated resuscitation therapy for cardiac arrest.[8−11]

Objectives

This study reviewed the role of ECPR in contemporary resuscitation care compared to no ECPR. A further objective was to quantitatively summarize the rates of long-term neurologically intact survival after adult cardiac arrest in any setting (in-hospital or out-of-hospital).

Materials and methods

This meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) and in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[51] Our review protocol was drafted and revised as necessary, before being registered in the International Prospective Register of Systematic Reviews (CRD42020171945) (https://www.crd.york.ac.uk/PROSPERO/).

The review question was formulated following the PICO framework (P-Populations/People/Patient/Problem, I-Intervention (s), C-Comparison, O-Outcome) and the Question Statement.[52] Question: Among adults (≥ 16 years) resuscitated from IHCA or OHCA (P) and treated with ECPR (I), compared to no ECPR and/or conventional CPR (C), what are the rates of long-term neurologically intact survival (O)?

Criteria for considering studies for this review

Types of study
All studies employing patient-level randomization or cluster randomization comparing ECPR vs. no ECPR and/or conventional CPR were considered for inclusion. We also considered observational analytic studies (cohort and case-control studies) with an appropriate control group published between January 1st, 2000, and January 31st, 2020.

A preliminary review suggested there would not be any relevant articles prior to the year 2000. We excluded any other type of study design.

Types of participant
We considered for inclusion adults suffering IHCA or OHCA, with resuscitation attempted by a bystander or healthcare provider. We excluded studies considering IHCA or OHCA due to trauma, hypothermia, and toxic substances, as the core interventions provided by healthcare providers (CPR and early defibrillation) are unlikely to be of significant benefit in such circumstances. We also excluded studies considering IHCA/OHCA in pediatrics and pregnancy. The exclusions were meant to reduce heterogeneity in the population while maintaining generalizability to most patients suffering cardiac arrest.

Types of intervention
We considered for inclusion studies comparing ECMO using pump-driven venous-arterial (VA) circuits vs. no ECPR and/or conventional CPR.

Types of outcome measure

Primary outcomes
The primary outcomes of interest were long-term neurologically intact survival after IHCA and OHCA, after IHCA, and after OHCA. Long-term time frames for neurologically intact survival (three months to two years) were combined into a single category, defined a priori as a Glasgow-Pittsburgh cerebral performance category (CPC) of 1 or 2, as measured by any validated scale.[53]

Search methods for identification of studies

Electronic searches
We used the PRESS (Peer Review of Electronic Search Strategies) checklist to develop the research strategy.[54] We searched the following databases on January 31st, 2020: The Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library (Issue 1 of 12, January 2020), MEDLINE (PubMed) (2000 to January 2020), Embase (Ovid) (2000 to January 2020), and Web of Science (2000 to January 2020), followed by a supplementary search on May 12th to ascertain that no new literature was published in the interim. We used relevant keywords and controlled vocabulary (e.g. medical subject headings). We also applied filters for MEDLINE and Embase terms to optimize search performance, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[55] We adapted the search strings devised for MEDLINE for use in searching other databases (Appendix A). All clinical studies published in English as full-text articles in indexed journals were considered for inclusion regardless of publication or publication status.

Searching other resources
We searched the following clinical trial registries for ongoing/unpublished randomized clinical trials (RCTs) on January 31st, 2020: The National Institutes of Health ongoing clinical trials register (www.clinicaltrial.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/). We searched the reference lists of included studies for further references and the abstracts of conference proceedings of the AHA and the ERC. We also increased reliance on web-based searching to identify additional studies.

Data collection and analysis

Selection of studies

Two investigators independently screened the titles and abstracts of all retrieved citations against the inclusion criteria. Studies that met the criteria were independently reviewed by the investigators. We used EndNote (X9.3, Clarivate Analytics) to manage the collected publications. Disagreements regarding inclusion/exclusion were resolved via discussion or by the decision of a third independent investigator. We used a Kappa coefficient to measure interrater reliability to determine the degree of agreement between the two investigators collecting studies for eligibility. The formula was entered into Microsoft Excel. In the case of a Kappa of 0.01−0.80 the third independent investigator reviewed all excluded full-text articles for eligibility to ensure optimized sensitivity.

Data extraction and management

Data extraction was performed using a standardized Excel form. It focused on identifying information on sample participants (demographic characteristics), study methods (setting, intervention, method of delivery), clinical parameters, outcome measures, and complications or adverse events. Any disagreements were resolved by discussion or by the decision of the third independent investigator.

PRISMA Flow Diagram
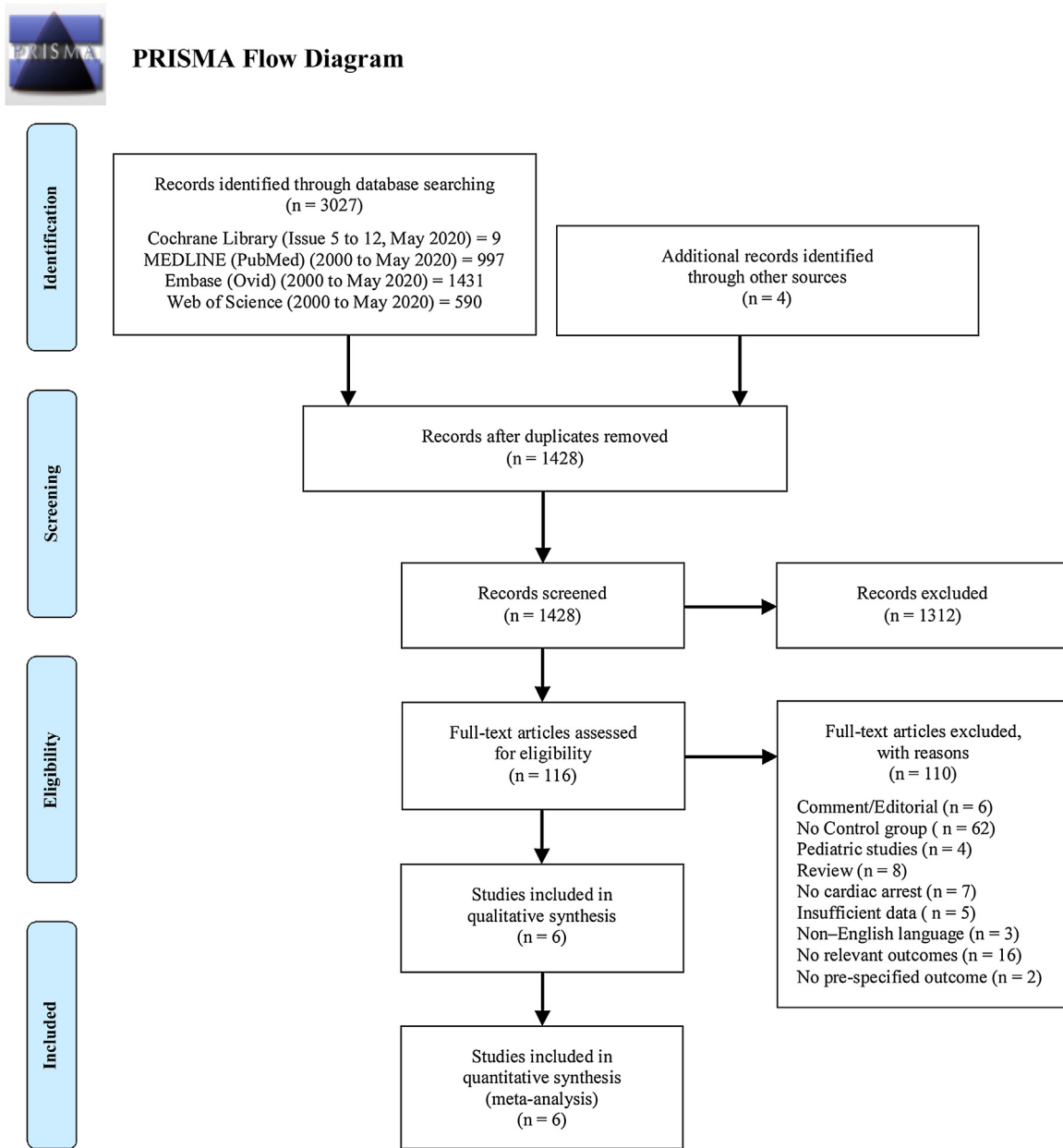
Fig. 1 – PRISMA flow diagram for systematic review of the use of ECPR vs. no ECPR and/or conventional CPR on long-term neurologically intact survival after adult cardiac arrest in any setting (in-hospital or out-of-hospital).
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6:e1000097.

Table 1 – Characteristics of studies included in the review.

Authors, year, country	Study design	Years of inclusion	No. of pts	Inclusion criteria/Criteria for ECPR	Exclusion criteria/Contraindication for ECPR	Primary endpoints/Additional endpoints
Chen et al. 2008[48] Taiwan	A single-center propensity-matched, pro-spective, cohort study.	2004−2006	172	Age 18−75 years, witnessed cardiac arrest, CPR for > 10 min, cardiac etiology. Only patients who underwent wit-nessed arrest of cardiac origin and CPR duration (defined as the interval from beginning CPR to ROSC or death) for more than 10 min were recruited in the study cohort.	CPR < 10 min, known severe irreversible brain damage, ter-minal malignancy, a traumatic origin with uncontrolled bleed-ing; non-cardiac arrest, signed DNR order.	Survival to hospital discharge and analysis was by intention to treat. Additional endpoints: ROSC, 24-hs, 3-days, 14-days, 30-days, and 6-months survival.
Kim et al. 2014[45] South Korea	A single-center propensity-matched, retro-spective, cohort study based on a prospective cohort.	2006−2013	499	Age ≥ 18 years, sudden cardiac arrest with presumed correct-able causes, witnessed cardiac arrest with or without bystander CPR, no-flow time (expected to be short, even for unwitnessed cardiac arrest). ECPR team was activated if above criteria were met and patient required prolonged CPR > 10 min as in-hospital CPR duration or when recurrently arrested in the ED after achieving sustained ROSC for at least 20 min.	Cardiac arrest due to a clearly uncorrectable cause, presence of a terminal illness or malig-nancy, suspected traumatic or-igin of arrest; no informed consent from family.	CPC of 1 or 2 at 3 months post-cardiac arrest. To find indica-tions for predicting good neu-rological outcome according to CPR duration and the optimal duration of CPR before con-sidering ECPR. Additional endpoints: Cause of death at 3-months.
Maekawa et al. 2013[46] Japan	A post hoc analysis of data from a single-center prospec-tive, cohort study, including propensity score matching.	2000−2004	162	Age ≥ 16 years, CPR duration > 20 min, witnessed, presumed cardiac origin. ECPR was initi-ated if ROSC did not occur or could not be maintained during transportation, if the patient was assessed to have good activi-ties of daily life before cardiac arrest, and if the cardiac arrest was clinically presumed as cardiac in origin by the patient's information reported by para-medics and rapid echocardio-graphic examination.	Previously signed DNR order, pronounced dead before hos-pital arrival. Contraindication for ECPR: Non-cardiac cause of arrest. Cardiac arrest was pre-sumed to be of cardiac origin unless it was known or likely to have been caused by trauma, submersion, hypothermia, drug overdose, asphyxia, exsangui-nation, or any other noncardiac cause including intracranial hemorrhage, acute aortic dis-section, and terminal malignancy.	Favorable neurologic status at 3-months after cardiac arrest. Determine potential predictors that can identify candidates for ECPR among patients with OHCA. Additional endpoints: ED survival.
Sakamoto et al. 2014[47] Japan	A multi-center prospective, co-hort study.	2008−2011	451	VF/VT on the initial electrocar-diogram, cardiac arrest on ar-rival to hospital with or without prehospital ROSC, arrival at hospital within 45 min of the emergency call or the cardiac arrest, no ROSC for 15 min after hospital arrival in spite of on-going CPR.	Age < 20 or > 75 years, poor level of activities of daily living prior to arrest, arrest of non-cardiac origin (i.e. trauma, drug intoxication, primary cerebral disorder, aortic dissection, ter-minal phase of cancer), core temperature < 30 °C, no in-formed consent from patient representatives.	Favorable neurologic status at 1-month and 6-months after OHCA, defined as the Glas-gow-Pittsburgh CPC of score of 1 or 2.
Shin et al. 2013[49] South Korea	A single-center propensity-matched, retro-spective, cohort study.	2003−2009	406	Prolonged arrest and no ROSC within 10−15 min after initiation of CPR, when ROSC could not be maintained due to recurrent arrest, or when recovery with-out ECMO support was unlikely due to known severe left ven-tricular dysfunction or coronary artery disease despite relatively short CPR duration.	Age > 80 years, previous se-vere neurological damage, current intracranial hemor-rhage, malignancy in the ter-minal stage, arrest of traumatic origin with uncontrolled bleed-ing, arrest of septic origin, irreversible multi-organ failure leading to cardiac arrest, and patients who signed DNR or-ders. Patients with CPR dura-tion of less than 10 min, unwitnessed arrest.	Survival at 2-years and neuro-logical outcomes. Neurological outcome was defined by the Modified Glasgow Outcome Score. Additional endpoints: Survival analysis for neurologi-cal outcomes at 6-months; 2-years follow-up was conducted for all survivors.

Table 1 *(continued)*

Authors, year, country	Study design	Years of inclusion	No. of pts	Inclusion criteria/Criteria for ECPR	Exclusion criteria/ Contraindication for ECPR	Primary endpoints/ Additional endpoints
Siao et al. 2015[50] Taiwan	A single-center retrospective, cohort study.	2011−2013	60	Age 18−75 years, cardiac arrest with initial VF and CPR initiated within 5 min (no-flow duration < 5 min), refractory VF defined as VF resistant to at least 3 defibrillations, 3 mg of epinephrine, 300 mg of amiodarone, and no ROSC achieved after CPR for more than 10 min.	Severe head trauma or severe acute active bleeding, severe sepsis, VF that developed during resuscitation for initial asystole or pulseless electrical activity, terminal stage of malignancy, any history of severe neurological deficits (including dementia, intracranial hemorrhage, or ischemic stroke and bedridden state).	Survival to discharge and neurologically intact survival; also looked at 1-year survival to discharge and favorable neurological outcome. Additional endpoints: ROSC.

Abbreviations: CPR = cardiopulmonary resuscitation; CPC = cerebral performance category; ECLS = extracorporeal life-support; ECMO = extracorporeal membrane oxygenation; ECPR = extracorporeal cardiopulmonary resuscitation; ED = emergency department; DNR = do-not-resuscitate; OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; VF = ventricular fibrillation; VT = ventricular tachycardia.
Notes: All studies compared ECPR vs. no ECPR while Shin et al. compared ECPR attempt vs. no ECPR attempt. Sakamoto et al. compared emergency departments with ECPR vs. emergency departments with no ECPR.

Assessment of risk of bias

Two investigators independently assessed the methodological qualities of each study using the Cochrane Collaboration Risk of in Non-randomized Studies of Interventions (ROBINS-I) tool.[56] Using this tool, seven domains are investigated for potential risk of bias, judged via signaling questions. Bias was assessed per study; each bias domain and overall risk of bias were classified as low, moderate, serious, or critical risk. Disagreements were resolved via discussion or by the decision of the third independent investigator.[56,57]

Measures of treatment effect

We calculated the risk ratios (RRs) and associated 95% confidence intervals (CIs) for each study to measure neurological outcomes, which were grouped into the categories of favorable neurological outcome (CPC) of 1 or 2 so they could be adapted for the meta-analysis. Pooled data were analyzed using the Mantel-Haenszel method and a two-sided p-value < 0.05 was considered statistically significant. We planned to use a random-effects model with appropriate caution in interpretation in the event of moderate or high heterogeneity; otherwise, we use the fixed-effect model. The pooled estimates of effect in the random-effects model presented the average effect of unadjusted long-term neurologically intact survival after IHCA and OHCA, IHCA, or OHCA treated by ECPR compared to no ECPR and/or conventional CPR. All analysis was performed using Review Manager (RevMan 5.3)[58] and followed the recommendations given in the Cochrane Handbook for Systematic Reviews of Interventions.[57]

Table 2 – Demographic and baseline clinical characteristics of the ECPR group and the CCPR group of studies included.

Authors, year, country	Patient groups (n)		Age (mean ± [SD]/ median [IQR])		Male, n (%)		Witnessed arrest, n (%)		Bystander CPR, n (%)		Arrest to CPR (min)*	
	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR
Chen et al. 2008[48] Taiwan	59	113	57.4±12.5	60.3±13.3	50 (85)	73 (65)	59 (100)	113 (100)	Not applicable	Not applicable	. . .	. . .
Kim et al. 2014[45] South Korea	55	444	53 (41−68)	69 (56−77)	41 (75)	285 (64)	43 (78)	328 (74)	23 (42)	151 (34)	7 (0−13)	8 (5−12)
Maekawa et al. 2013[46] Japan	53	109	54 (47−60)	71 (59−80)	44 (83)	79 (73)	. . .	. . .	29 (55)	42 (39)	6 (2−9)	7 (3−10)
Sakamoto et al. 2014[47] Japan	258	193	56 (NR)	58 (NR)	235 (90)	172 (89)	186 (72)	151 (78)	127 (49)	90 (46)	. . .	. . .
Shin et al. 2013[49] South Korea	85	321	59.9±15.3	61.6±14.2	53 (62)	201 (63)	85 (100)	321 (100)	Not applicable	Not applicable	. . .	. . .
Siao et al. 2015[50] Taiwan	20	40	54.5±11.9	60.3±11.2	18 (90)	28 (70)	. . .	. . .	Not applicable	Not applicable	1−4.5	. . .

Abbreviations: CPR = cardiopulmonary resuscitation; CCPR = conventional cardiopulmonary resuscitation; ECPR = extracorporeal cardiopulmonary resuscitation.
Notes: Total percentages refer to studies with available data and continuous variables reported as mean ± standard deviation (SD) or as median interquartile range (IQR). Proportions - No. (%) of studies performing propensity score matching refer to the unmatched pre-arrest and post-arrest clinical characteristics and outcomes.
Notes: None of the patients received mechanical cardiopulmonary resuscitation (mCPR).
*Reported as the interval from collapse to initiation of CPR or no-flow duration.

Table 3 – Baseline clinical characteristics and variables of the ECPR group and the CCPR group of studies included.

Authors, year, country	Asystole, n (%) ECPR	Asystole, n (%) CCPR	PEA, n (%) ECPR	PEA, n (%) CCPR	VF/VT, n (%) ECPR	VF/VT, n (%) CCPR	CPR duration (min) ECPR	CPR duration (min) CCPR	CPR to ECMO duration (min) ECPR	CPR to ECMO duration (min) CCPR	ROSC (ROSB), n (%) ECPR	ROSC (ROSB), n (%) CCPR	Presume cardiac etiology, n (%) ECPR	Presume cardiac etiology, n (%) CCPR
Chen et al. 2008[48] Taiwan	13 (22)	31 (27)	17 (29)	46 (41)	29 (42)	36 (32)	53±37	43±31	…	…	55 (93)	63 (56)	59 (100)	113 (100)
Kim et al. 2014[45] South Korea	14 (26)	268 (60)	10 (18)	91 (21)	31 (56)	85 (19)	62 (47–89)	35 (21–50)	1.5 (0.6–6.4)*	…	44 (80)	212 (48)	49 (89)	267 (62)
Maekawa et al. 2013[46] Japan	…	…	…	…	32 (60)	24 (22)	49 (41–59)	56 (47–66)	…	…	…	…	…	…
Sakamoto et al. 2014[47] Japan	…	…	…	…	258 (100)	193 (100)	…	…	…	…	…	…	226 (87)	150 (77)
Shin et al. 2013[49] South Korea	10 (12)	47 (15)	50 (59)	201 (63)	25 (29)	73 (23)	42±26	41±37	…	…	64 (75)	167 (52)	63 (74)	182 (57)
Siao et al. 2015[50] Taiwan	…	…	…	…	20 (100)	40 (100)	70±50	34±18	49±43.9	…	19 (95)	19 (48)	16 (80)	21 (53)

Abbreviations: CPR = cardiopulmonary resuscitation; CCPR = conventional cardiopulmonary resuscitation; ECPR = extracorporeal cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; PEA = pulseless electrical activity; ROSB = return of spontaneous heartbeat; ROSC = return of spontaneous circulation; VF = ventricular fibrillation; VT = ventricular tachycardia.

Notes: Total percentages refer to studies with available data and continuous variables reported as mean ±SD or as median IQR.

Studies reporting in-hospital cardiac arrest did not report collapsed-time to CPR though it was considered to be minimal as per inclusion criteria.

CPR duration was defined as the interval between initiation of CPR and ROSC or death in the CCPR group, and as the interval between initiation of CPR and ECLS implantation in the ECPR group. Return of spontaneous heartbeat was identified by echocardiography in the ECPR group and by palpable central pulse or peripheral arterial pulse in the CCPR group.

*The median time interval from ROSC to ECPR implantation was 1.5 (range 0.6–6.4) hours.

Dealing with missing data

We planned to contact authors of included studies in the event that not all relevant data were presented in the text of a study. Missing relevant statistical parameters and variance measures were calculated if data permitted.

Assessment of heterogeneity

We assessed heterogeneity across studies by inspecting the detailed clinical characteristics of the included studies. We evaluated the presence and degree of heterogeneity using the Mantel-Haenszel Chi^2 test and the I^2 statistic for each outcome. We considered statistically significant heterogeneity a p-value ≤ 0.10 for the Mantel-Haenszel Chi^2 test or values $> 50\%$ using the I^2 statistic.[57]

Assessment of reporting biases

We planned to use a funnel plot to assess publication bias and test for funnel plot asymmetry if more than 10 studies were included.[59]

Subgroup analysis

We planned to perform subgroup analyses if sufficient data were available (i.e. from three or more studies). Our subgroup analysis of interest included the following variables: time interval from onset of cardiac arrest to initiation of CPR (no-flow time ≤ 5 min or > 5 min); time interval from initiation of CPR to return of spontaneous circulation (ROSC) by ECMO-facilitated resuscitation or termination of resuscitation (low flow time ≤ 60 min or > 60 min).[60]

Sensitivity analysis

We planned to perform a sensitivity analysis for primary outcomes if a sufficient number of studies reported outcomes, to determine if a high risk of bias affected results. We planned to perform sensitivity analyses by excluding studies with high risk of bias and studies with unclear risk of bias. We also planned to perform sensitivity analyses comparing fixed-effect pooled estimates or 95% CIs vs. random-effects pooled estimates or 95% CIs.

Summary of findings

We created a summary of findings table for the outcomes of interest. We used GRADE principles (Grades of Recommendation, Assessment, Development and Evaluation) to appraise the quality/certainty of evidence associated with specific outcomes.[61,62] The quality of a body of evidence reflects within-study risk of bias, directness of evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias. Evidence quality for each specific outcome was classified as high, moderate, low, or very low quality. We used the methods recommended in the Cochrane Handbook and GRADEpro GDT for these analyses.[57,63]

Results

Study selection

The initial search returned nine citations from CENTRAL, 997 citations from MEDLINE, 1431 citations from Embase, and 550 citations from Web of Science. Additional papers were identified by searching Google Scholar or through bibliographic review. After duplicates were eliminated, 1428 citations remained for screening, of which 116 were eligible for full-text review. We excluded 110 papers at this stage, because they did not meet the study inclusion criteria after review of the

Table 4 – Baseline clinical characteristics and outcomes of the ECPR group and the CCPR group of studies included.

Authors, year, country	Serum lactate/Arterial pH (mean ± [SD]/median [IQR])		Coronary angiography, n (%)		Reperfusion therapy/ PCI/CABG, n (%)		ACS/AMI, n (%)		Therapeutic hypothermia, n (%)		Neurological outcome (CPC 1−2) at discharge, 30-day and/or long-term neurological outcome, n (%)	
	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR	ECPR	CCPR
Chen et al. 2008[48] Taiwan	Lactate: NR pH: 12.0 (2.4−39.7)*	Lactate: NR pH: 3.7 (1.1−20)*	. . .	. . .	26 (44)	6 (6)	37 (63)	80 (71)	No applied	No applied	Discharge: 14 (24) 30-day: 14 (24) 1-year: 9 (15)	Discharge: 12 (11) 30-day: 12 (11) 1 year: 10 (9)
Kim et al. 2014[45] South Korea	Lactate: 17.7 (8.8−16.0)† pH: 6.98 (6.86−7.05)†	Lactate: 10.8 (7.3−14.0)† pH: 6.94 (8.8−16.0)†	39/44 (89)	11/15 (73)‡	29 (94)	3 (100)	36/52 (69)	9/52 (17)	17 (31)	71 (16)	Discharge: 8 (14) 30-day: 8 (15) 3-months: 8 (15)	Discharge: 36 (8) 30-day: 36 (8) 3-months: 36 (8)
Maekawa et al. 2013[46] Japan	Lactate: NR pH: NR	Lactate: NR pH: NR	. . .	. . .	21 (40)§	6 (6)§	. . .	. . .	26 (49)‖	7 (6)‖	Discharge: NR 30-day: NR 3 months: 15 (28)	Discharge: NR 30-day: NR 3-months: 5 (5)
Sakamoto et al. 2014[47] Japan	Lactate: NR pH: NR	Lactate: NR pH: NR	157/177 (89)‖	25/37 (68)‖	97/177 (55)‖	21/37 (57)‖	165 (64)	115 (59)	162/167 (92)	20/37 (54)	Discharge: NR 30-day: 32 (12) 6-months: 29 (11)	Discharge: NR 30-day: 3 (1.6) 6-months: 5 (3)
Shin et al. 2013[49] South Korea	Lactate: NR pH: NR	Lactate: NR pH: NR	. . .	. . .	18 (21)§	11 (3)§	38 (45)	82 (26)	No applied	No applied	Discharge: NR 30-day: 24 (28)# 2-years: 22 (26)#	Discharge: NR 30-day: 24 (8)# 2-years: 22 (7)#
Siao et al. 2015[50] Taiwan	Lactate: 8.90 (2.29) pH: NR	Lactate: 8.25 (2.29) pH: NR	. . .	. . .	12 (60)§,¶	16 (40)§,¶	12 (60)	16 (40)	9 (45)‖	9 (23)‖	Discharge: 8 (40) 30-day: NR 1-year: 8 (40)	Discharge: 3 (8) 30-day: NR 1-year: 3 (8)

Abbreviations: ACS = acute coronary syndrome; AMI = acute myocardial infarction; CPR = cardiopulmonary resuscitation; CCPR = conventional cardiopulmonary resuscitation; CPC = cerebral performance category; ECPR = extracorporeal cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; GABC = coronary artery bypass grafting; PCI = percutaneous coronary intervention; pH = measured acid-base balance of the blood; ROSB = return of spontaneous heartbeat; ROSC = return of spontaneous circulation.

Notes: Total percentages refer to studies with available data.

Neurologically intact survival (i.e. long-term [three months to two years]) were combined into a single category.

* Available maximal lactic acid in 24-h period.

† Measured in 48 ECPR patients and 332 CCPR patients.

‡ In 15 suspected ACS patients with ROSC (≥ 20 min).

§ Reported as primary PCI.

‖ The contents of treatments given to 214 patients (92% of 177 patients in the ECPR group and 54% of 37 patients in the CCPR group), who were alive at 24 h after cardiac arrest. The frequencies of introducing TH and performing intra-aortic balloon pump were significantly higher in the ECPR group.

¶ Emergency coronary angiography was performed by cardiologist if acute myocardial infarction was suspected.

‖ Therapeutic hypothermia was considered when the patients remain comatose after ROSB (ECPR group) or ROSC (CCPR group) and decided by the ICU attending physicians.

Minimal neurological impairment was defined as a Modified Glasgow Outcome Score (MGOS) ≥ 4.

Table 5 – Clinical course and complications of the ECPR group and the CCPR group of studies included.

Authors, year, country	Patients (n) ECLS	Patients (n) CCPR	Weaned off cardiac assist device (ECMO) (%) ECLS	Weaned off cardiac assist device (ECMO) (%) CCPR	Bridge to short/long term IABP/VAD or HTP (%) ECLS	Bridge to short/long term IABP/VAD or HTP (%) CCPR	Bleeding (%) ECLS	Bleeding (%) CCPR	Peripheral vessel complications (%) ECLS	Peripheral vessel complications (%) CCPR	Blood transfusions (pRBC/FFP) (%) ECLS	Blood transfusions (pRBC/FFP) (%) CCPR	Duration of ECMO (hrs) ECLS	Duration of ECMO (hrs) CCPR
Chen et al. 2008[48] Taiwan	59	113	29 (49)*	Not applicable	IABP: NR VAD: 5.1 HTP: 8.1	. . .	. . .	. . .	. . .	. . .	pRBC: NR FFP: NR	. . .	110±28	. . .
Kim et al. 2014[45] South Korea	55	444	8 (15)†	Not applicable	IABP: NR VAD: 5.1 HTP: 8.1	. . .	27‡	. . .	. . .	. . .	pRBC§ FFP: NR	. . .	43.6 (29.7−92.8)†	. . .
Maekawa et al. 2013[46] Japan	53	109	. . .	Not applicable	IABP: 51 VAD: NR HTP: NR	IABP: 9.2	33‖	. . .	15.4	. . .	pRBC: NR FFP: NR	. . .	. . .	. . .
Sakamoto et al. 2014[47] Japan	260	194	. . .	Not applicable	IABP: 63 VAD: NR HTP: NR	IABP: 12	. . . ¶	. . .	. . .	. . .	pRBC: NR FFP: NR	. . .	. . .	. . .
Shin et al. 2013[49] South Korea	85	321	. . .	Not applicable	IABP: NR VAD: 0.0 HTP: 2.4	VAD: 0.0 HTP: 0.9	. . .	. . .	. . .	. . .	pRBC: NR FFP: NR	. . .	. . .	. . .
Siao et al. 2015[50] Taiwan	20	40	. . .	Not applicable	IABP: 50 VAD: NR HTP: NR	IABP: 25	. . .	. . .	. . .	. . .	pRBC: NR FFP: NR	. . .	79.7±35.1	. . .

Abbreviations: CCPR = conventional cardiopulmonary resuscitation; ECMO = extracorporeal membrane oxygenation; ECPR = extracorporeal cardiopulmonary resuscitation; FFP = fresh frozen plasma; HTP = heart transplant; IABP = intra-aortic balloon pumping; pRBC = packed red blood cells; VAD = ventricular assist device.

NotesTotal percentages refer to studies with available data and continuous variables reported as mean±SD or as median IQR.

* Weaning, defined as successful separation from extracorporeal life-support without mortality in 12h, was not attempted until 72h after initiation. Ventricular assist device and heart transplantation were alternatives in the absence of contraindications when weaning was unsuccessful in 5−7 days.

† Successful weaning and duration of ECMO in patients with a good neurological outcome (measured as a CPC score of 1 or 2).

‡ Reported bleeding at access site 27.3%, leg ischemia 6.8%, circuit failure 0%, intracranial hemorrhage/stroke 2.3%, and acute kidney injury 1.9%.

§ Amount of transfused pRBC5 (3−12) in patient with a CPC 1, 2 (n=8) and pRBC: 5 (1−10) in patient with a CPC 3−5 (n=44).

‖ Reported bleeding at access site 32.7%, leg ischemia requiring reperfusion 15.4%, unsuccessful cannulation 1.9%, infection 7.7%, and compartment syndrome requiring fasciotomy 1.9%.

¶ During the study period, several ECMO-related complications were reported. Bleeding and hematoma of insertion sites were relatively common. Other rare complications were vascular injury, catheter infection, limb ischemia, gastrointestinal bleeding, hemolysis, and stroke. Transfusion of pRBC and FFP were performed but total percentages were not reported.

Table 6 – Configuration and component set-up of the extracorporeal membrane oxygenation system of studies included.

Authors, year, country	Centrifugal pump	Cannulation procedure and strategy	Arterial catheter	Venous catheter	Anterograde reperfusion catheter	Initiation of pump flow rate	ACT aim therapeutic range
Chen et al. 2008[48] Taiwan	Bio-Pump, Medtronic, Anaheim, USA	Percutaneous femoral cannulation was preferred in most cases	Not specified	Not specified	Yes*	50−100 mL/kg/min	160−180 s (220 s during weaning)
Kim et al. 2014[45] South Korea	Twin-pulse life support (T-PLS), New Heartbio, Korea Capiox Emergency Bypass System, Terumo Corp, Tokyo, Japan	Percutaneous femoral artery and vein using the Seldinger technique	15−17 Fr	21−23 Fr	. . .	2.5−3.0 L/min	200−220 s
Maekawa et al. 2013[46] Japan	Capiox Emergency Bypass System, Terumo Corp, Tokyo, Japan	Percutaneous femoral artery and vein cannulation. Femoral cut down procedures were not performed	15−17 Fr	19−21 Fr	As necessary	50−60 mL/min/kg	. . .
Sakamoto et al. 2014[47] Japan	Several types of centrifugal pumps were used	Percutaneous femoral artery and vein (or any other method)	Not specified	Not specified	As necessary	Maximal flow rate (target: 4 L/min or above)	1.5−2.5 times normal
Shin et al. 2013[49] South Korea	Capiox Emergency Bypass System, Terumo Corp, Tokyo, Japan	Percutaneously in a majority of case or surgically in challenging cases	14−21 Fr	21−28 Fr	Yes†	2.2 L/min/BSA (m^2)‡	. . .
Siao et al. 2015[50] Taiwan	Bio-Pump, Medtronic, Anaheim, USA	Femoral cannulation in the emergency department	Not specified	Not specified	. . .	A minimum flow of 2 L/min	180−220 s

Abbreviations: ACT = activated clotting time; BSA = body surface area.

Notes: Only one study reported unsuccessful cannulation or if cannulation strategy was performed by emergent cannulation, cannulation guidance by ultrasound or combination of ultrasound and fluoroscopy guided cannulation. This study used ultrasound-guided catheter insertion in the emergency department and fluoroscope-guided catheter insertion in the catheterization room.[45]

* No bridging tube between the arterial and venous lines was applied. To avoid possible distal malperfusion an antegrade reperfusion catheter for distal limb perfusion was applied when the mean pressure of the superficial femoral artery was below 50 mmHg.

† A bypass catheter was inserted into the femoral artery to facilitate distal limb perfusion in the event of leg ischemia after arterial cannulation.

‡ The flow rate was set above 2.2 L/min/body surface area (m^2) initially, and was adjusted subsequently to maintain a mean arterial pressure above 65 mm Hg.

text. These studies are listed in Appendix B. The interrater reliability between the reviewers of positive agreement was 0%, negative agreement was 94%, kappa was 0.33. Fig. 1 shows a PRISMA diagram of the study selection process. We included six cohort studies comprising 1750 participants in the review. Of these, 530 participants (30.3%) received the intervention; 91 (17.2%) survived with long-term neurologically intact survival.[45−50] Three studies were in an out-of-hospital setting,[45−47] two took place in-hospital,[48,49] and one had both in-hospital and out-of-hospital components.[50] Tables 1−4 provide an overview of included studies. The search of clinicaltrials.gov identified several ongoing clinical trials of ECPR for cardiac arrest; overviews of these are provided in Appendix C.

Included studies

Two studies were prospective cohort,[47,48] one study performed post hoc analysis of a previously published, prospective single-center study,[46] and the last three were retrospective cohort.[45−50] Four studies performed propensity score matched analysis[45−49] and two used a logistic regression analysis.[47,50] Two studies were conducted in South Korea,[45,49] two in Taiwan,[48,50] and two in Japan.[47,46] Years of patient inclusion ranged from 2000 to 2013. Eligibility criteria for ECPR varied across studies; an overview is provided in Appendix D. The average age

of patients exposed to the intervention ranged from 53 to 60 and 58 to 69 in the control group. In the ECPR group 90.0% of patients were male vs. 70.0% in the control group. Witnessed arrest was present in 457 of 474 patients (96.4%) in the ECPR group and 933 of 1071 patients (87.1%) in the control group. Bystander CPR was performed in 179 of 366 patients (47.3%) in the ECPR group and in 283 of 366 patients (77.3%) in the control group. The initial documented heart rhythm of ventricular fibrillation was reported in 117 of 252 patients (44.4%) in the ECPR group and in 218 of 987 patients (22.1%) in the control group. Overall collapse to ECPR times was not reported. Three studies reported no-flow duration (collapse to initial CPR),[45−50] one reported CPR to ECMO duration,[50] and another reported time interval from ROSC to ECMO implantation.[45] Two studies reported neurologically intact survival at three months,[45,47] one at six months,[47] two at one year,[48,50] and one at two years.[49] The rates of long-term neurologically intact survival after IHCA and OHCA, IHCA, or OHCA of ECPR-treated patients were 15.5%, 22.7%, and 12.3%, respectively. Conversely, the rates of long-term neurologically intact survival after IHCA and OHCA, IHCA, or OHCA treated with conventional CPR were 6.2%, 6.8%, and 5.9%, respectively.[45−50] Five studies defined favorable neurological outcome as a Cerebral Performance Category score of 1−2.[45−50] One study defined minimal neurological impairment as a Modified Glasgow Outcome Score (MGOS) $\geq$ 4.[49] No studies specifically assessed

adverse events. An overview of the clinical course, complications, and circuit configuration and setup is provided in Tables 5–6.

Risk of bias in included studies

We present details of our risk of bias judgments in the risk of bias summary table. Based on the ROBINS-I tool, all studies were deemed to have an overall serious risk of bias, which could also be considered critical, with confounding being the primary source of bias. Additional details of bias assessments using the ROBINS-I tool are provided in eTable 1 in the Supplementary Contents.

Primary outcomes

Long-term neurologically intact survival after cardiac arrest occurred in 82 of 530 patients (15.5%) in the ECPR group and in 76 of 1220 patients (6.2%) in the control group. Statistical heterogeneity among these studies was not significant according to the Chi^2 test and the I^2 statistic (Chi^2=6.90, degrees of freedom (df)=5, p-value 0.23, I^2=28%). The pooled results for cardiac arrest in any setting show that ECPR compared to no ECPR and/or conventional CPR is likely associated with improved long-term neurologically intact survival after IHCA and OHCA (RR 3.11, 95% CI 2.06–4.69, p < 0.00001; 6 studies, 1750 participants; an increase from 62 to 194 per 1000, 95% CI 128–292; Fig. 2) (GRADE: Very low quality; downgraded for serious risk of bias).[45–50]

Long-term neurologically intact survival after IHCA occurred in 37 of 164 patients (22.6%) in the ECPR group and in 32 of 474 patients (6.8%) in the control group. Statistical heterogeneity among these studies was moderate according to the Chi^2 test and the I^2 statistic (Chi^2=3.28, df=2, p-value 0.19, I^2=39%). The pooled results for in-hospital arrest show that ECPR compared to no ECPR and/or conventional CPR is likely associated with improved long-term neurologically intact survival after IHCA (RR 3.21, 95% CI 1.74 –5.94, p < 0.0002; 3 studies, 638 participants; an increase from 68 to 217 per 1000, 95% CI 117–401; Fig. 2) (GRADE: Very low quality; downgraded for serious risk of bias).[48–50]

Long-term neurologically intact survival after OHCA occurred in 45 of 366 patients (12.3%) in the ECPR group and in 44 of 746 patients (5.9%) in the control group. Statistical heterogeneity among these studies was moderate according to the Chi^2 test and the I^2 statistic (Chi^2=3.61, df=2, p-value 0.16, I^2=45%). The pooled results for out-of-hospital arrest showed that ECPR compared to no ECPR and/or conventional CPR is likely associated with improved long-term neurologically intact survival after OHCA (RR 3.11, 95% CI 1.50 –6.47, p < 0.002; 3 studies, 1112 participants; an increase from 59 to 183 per 1000, 95% CI 88–382; Fig. 2) (GRADE: Very low quality; downgraded for serious risk of bias).[45–47]

Assessment of reporting biases

We did not test for publication bias using a funnel plot or other analytical methods because fewer than 10 studies were included.[59]

Summary of findings table and GRADE assessment

We created a summary of findings table for the outcomes of interest. Based on the GRADE criteria, the overall quality of the evidence was graded very low quality. We downgraded the overall quality to very low due to a serious risk of bias. A summary of findings and GRADE assessment is provided in eTable 2 in the Supplementary Contents.

Subgroup analysis

All studies included participants with non-traumatic cardiac arrest; however, few studies reported subgroup data according to time periods (i.e. no-flow time, low flow time). We performed no pre-defined subgroup analyses or investigations of heterogeneity due to insufficient data.

Sensitivity analysis

We were unable to perform the planned sensitivity analyses due to the small number of included studies.

Discussion

We identified a limited number of studies comparing the use of ECPR vs. no ECPR and/or conventional CPR in terms of long-term neurologically intact survival after adult IHCA or OHCA. Six cohort studies met our inclusion criteria, totaling 1750 cardiac arrest patients. Of these, 530 (30.3%) received the intervention; 91 (17.2%) survived with long-term neurologically intact survival.[45–50] The studies were non-randomized, prospective or retrospective cohorts; some used propensity score matching.[45,46,48,49] Some of the studies provided adjusted data; however, the included covariates were not sufficient to significantly reduce the risk of bias. Current evidence for the use of ECPR for cardiac arrest is limited by clinical heterogeneity and paucity of evidence at the level of RCTs, but we identified that the evidence is more in favor of ECPR than the comparator group (conventional CPR). There was a moderate degree of heterogeneity in our pooled analyses. We used a random-effects model for pooled analyses to account for these differences. No currently available RCT has investigated ECMO in the context of ECPR for cardiac arrest, though several are ongoing, as noted on the International Clinical Trials Registry Platform. Our analysis suggests that the risk of bias for individual studies was serious, which could also be considered critical. Based on GRADE criteria, the overall quality of evidence was very low across all outcomes, with the quality of evidence downgraded for serious risk of bias, with confounding being the primary source of bias.
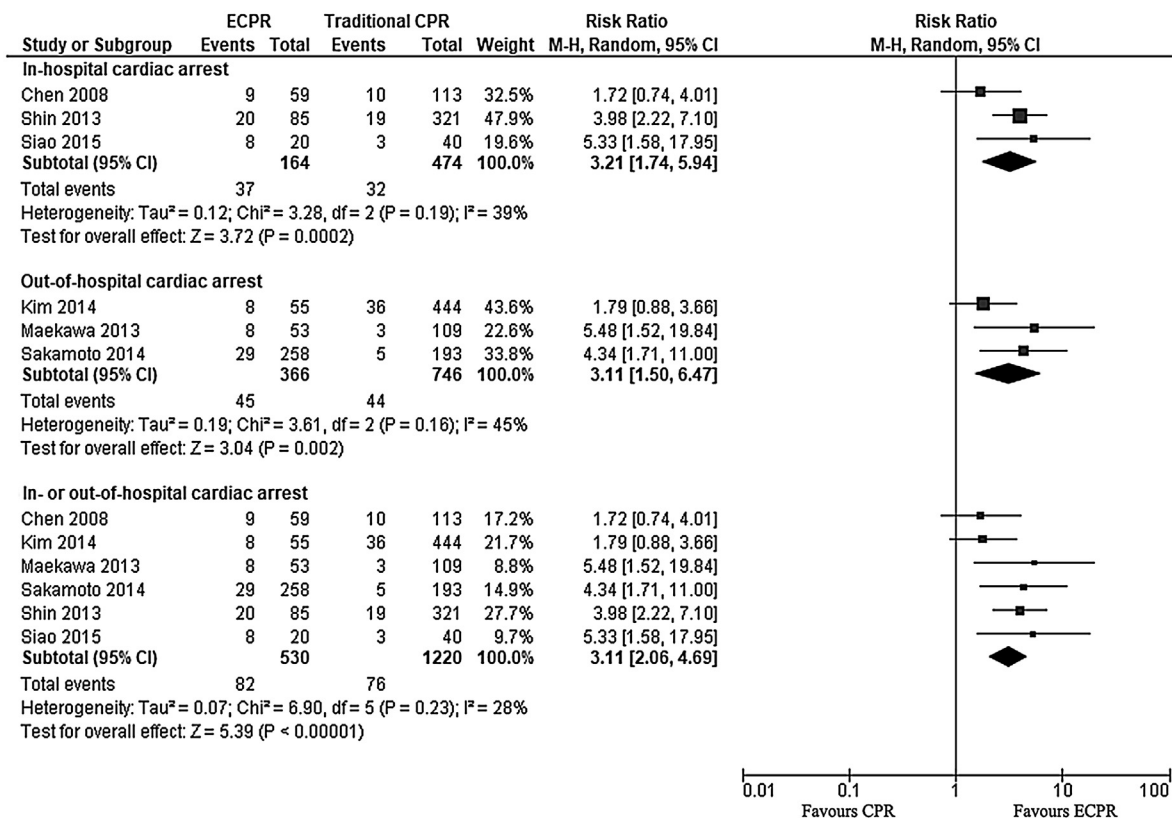
The International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support Task Force recently performed a systematic review comparing the use of ECPR vs. manual or mechanical CPR for adults and children following cardiac arrest. The results of the studies included in their review were mixed and the quality of evidence was overall assessed as very low and at high risk of bias.[64] Subsequently, the ILCOR has suggested ECPR may be considered a rescue therapy for selected patients with cardiac arrest when conventional CPR fails in settings where this can be implemented (weak recommendation, very low certainty of evidence).[64] The inclusion criteria of our review differ from the ILCOR review as we restricted our analyses to long-term neurologically intact survival and we separated and pooled the data after adult cardiac arrest in any setting (in-hospital or out-of-hospital). In our review the overall individual and pooled estimates and 95% CIs for the random-effects model examining long-term neurologically intact survival after IHCA and OHCA, IHCA, or OHCA are more in favor of ECPR than conventional CPR.[45–50] Our analysis suggests that the treatment effect (or effect size) is consistent with the findings of most primary studies.[45–50] These results are consistent with previous systematic reviews and meta-analyses, meaning that

Data and analyses

Review: Long-term neurological intact survival after ECPR for adult in-hospital or out-of-hospital cardiac arrest
Comparison: ECPR therapy vs. no ECPR
Outcome: Long-term neurologically intact survival

Study or Subgroup	ECPR Events	Total	Traditional CPR Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
In-hospital cardiac arrest						
Chen 2008	9	59	10	113	32.5%	1.72 [0.74, 4.01]
Shin 2013	20	85	19	321	47.9%	3.98 [2.22, 7.10]
Siao 2015	8	20	3	40	19.6%	5.33 [1.58, 17.95]
Subtotal (95% CI)		164		474	100.0%	3.21 [1.74, 5.94]
Total events	37		32			

Heterogeneity: Tau² = 0.12; Chi² = 3.28, df = 2 (P = 0.19); I² = 39%
Test for overall effect: Z = 3.72 (P = 0.0002)

Study or Subgroup	ECPR Events	Total	Traditional CPR Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Out-of-hospital cardiac arrest						
Kim 2014	8	55	36	444	43.6%	1.79 [0.88, 3.66]
Maekawa 2013	8	53	3	109	22.6%	5.48 [1.52, 19.84]
Sakamoto 2014	29	258	5	193	33.8%	4.34 [1.71, 11.00]
Subtotal (95% CI)		366		746	100.0%	3.11 [1.50, 6.47]
Total events	45		44			

Heterogeneity: Tau² = 0.19; Chi² = 3.61, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 3.04 (P = 0.002)

Study or Subgroup	ECPR Events	Total	Traditional CPR Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
In- or out-of-hospital cardiac arrest						
Chen 2008	9	59	10	113	17.2%	1.72 [0.74, 4.01]
Kim 2014	8	55	36	444	21.7%	1.79 [0.88, 3.66]
Maekawa 2013	8	53	3	109	8.8%	5.48 [1.52, 19.84]
Sakamoto 2014	29	258	5	193	14.9%	4.34 [1.71, 11.00]
Shin 2013	20	85	19	321	27.7%	3.98 [2.22, 7.10]
Siao 2015	8	20	3	40	9.7%	5.33 [1.58, 17.95]
Subtotal (95% CI)		530		1220	100.0%	3.11 [2.06, 4.69]
Total events	82		76			

Heterogeneity: Tau² = 0.07; Chi² = 6.90, df = 5 (P = 0.23); I² = 28%
Test for overall effect: Z = 5.39 (P < 0.00001)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours CPR — Favours ECPR

Comparison – Pooled risk ratios with 95% confidence intervals comparing ECPR therapy vs. no ECPR

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
Long-term neurologically intact survival after in-hospital cardiac arrest	3	638	Risk Ratio (M□H, Random, 95% CI)	3.21 [1.74–5.94]
Long-term neurologically intact survival after out-of-hospital cardiac arrest	3	1112	Risk Ratio (M□H, Random, 95% CI)	3.11 [1.50–6.47]
Long-term neurologically intact survival after in-hospital or out-of-hospital cardiac arrest	6	1750	Risk Ratio (M□H, Random, 95% CI)	3.11 [2.06–4.69]

Fig. 2 – Forest plot of comparison of long-term neurological intact survival after adult cardiac arrest. Abbreviations: CI = confidence interval; event = number of patient with outcomes; total = number of participants at risk; df = degree of freedom; I² = indicate the percentage of total variation across the studies that is due to heterogeneity rather than change; MH = stands for the Mantel-Haenszel method. The result and its 95% CI are presented by a diamond, with the risk ratio (95% CI) and its statistical significance given alongside. Squares or diamonds to the right of the solid vertical line indicate benefit with the intervention (ECPR) over the comparator group (no ECPR), but this is conventionally significant (p < 0.05) only if the horizontal line or diamond does no overlap the solid vertical line. Neurologically intact survival (i.e. long-term [three months to two years]) were combined into a single category.

the strategy of ECPR has resulted in functionally favorable survival rates ranging from 10% to 45%,[65–73] provided that cardiac arrest patients present with initial shockable cardiac rhythm, shorter CPR duration, higher admission arterial pH, and lower admission serum lactate level.[14,65] The ELSO Registry reports 29.0% survival to discharge/transfer in those treated with ECPR. This indicates the current clinical interest in ECPR for cardiac arrest patients.[12] ECPR thus seems to be a valuable option in selected cases.[10,11]

Patients receiving ECPR in this review were more likely to be male, younger than 75 years, have potentially reversible conditions, suffer from acute coronary syndrome, and to undergo emergency cardiac catheterization and, when necessary, coronary revascularization.[45–50] All of these factors are known to be associated with increased survival to discharge and neurologically intact survival. Outcomes of ongoing RCTs will clarify the role of ECPR in this particular population. When ECMO is used as ECPR, efforts should be made to select patients who

would benefit from the intervention and to minimize the duration of CPR to ECMO flow, as both are critical determinants of favorable outcomes.[14,65] ECMO should be initiated expeditiously in potentially reversible cases of refractory IHCA or OHCA, regardless of whether ROSC has been achieved, with manual and/or mechanical chest compressions to facilitate return of ROSC and to support further resuscitation efforts, including early coronary angiography and percutaneous coronary intervention (PCI) in selected patients with a suspected or obvious cardiac cause of cardiac arrest.[10,11] Further effort should be made to evaluate bundle treatment options used during ECPR, including coronary catheterization laboratory (CCL) (i.e. PCI, coronary artery bypass grafting),[16,17] CCL and target temperature management (TTM),[18−45,46] CCL and intra-aortic balloon pump (IABP),[24] and CCL, IABP, and TTM.[25−46,47] The development of practices associated with success, like creating large, feasible, regional or state-wide integrated resuscitation networks similar to the Minnesota Resuscitation Consortium should be a priority (i.e. the University of Minnesota refractory VF/VT ECPR protocol for OHCA), with the goal of overcoming knowledge gaps and improving outcomes in individuals who would have otherwise died (Appendix E).[26,27]

Limitations

Our review should be interpreted in the context of certain limitations. This review was limited to articles from four databases published in English between January 1st, 2000, and January 31st, 2020. This review aimed to identify the most recent and relevant articles, and therefore we excluded older publications; our preliminary review suggested there would be no relevant articles prior to 2000. While we took steps to ensure all relevant articles were included, it is possible some were missed due to the selection of databases, search terms, and language limitations. Therefore, there is an acknowledged risk of bias in article selection and interpretation. Most of the included studies were non-randomized and prospective or retrospective cohort design, single-center, and had high risk of bias, in particular confounding bias, potentially limiting internal validity. There was an attempt to adjust for confounding factors in the design and/or analysis of each study, yet the observed association between exposure and outcome is still dominated by residual confounding effects, potentially limiting our analysis. A major limitation of this study is the pooling unadjusted results of some heterogeneous outcomes. Furthermore, all studies were from Asia, thus are unlikely to reflect systems of care in North America and Europe, limiting comparability. Outcomes reported among controls are also lower than those in other developed countries, where the rate of bystander CPR is considerably higher than in Asia. All of which potentially limits applicability, generalizability, external validity, and possible considerations for indirectness. Our ability to draw conclusions is thus severely limited by the quality of the primary data. The well-recognized weaknesses of observational studies mean that no reliable conclusions can be drawn from the primary data, which carries a high risk of bias and may yield precise but spurious results when combined.[73] This thus suggests the importance of high quality research into the feasibility and patient-centered outcomes of using ECPR in novel settings, such as via EMS-based or ED-based large randomized trials, to further investigate the effectiveness of ECPR for cardiac arrest.

Since this review was accepted, in October 2020, we searched for recent studies on the topic. The Advanced Reperfusion Strategies for Refractory Cardiac Arrest (ARREST) trial has recently been published. The trial evaluated the initiation of ECMO in the cardiac catheterization laboratory compared with Advanced cardiac life support (ACLS) among patients with OHCA and refractory VF/VT.[74] The primary outcome, survival to hospital discharge, occurred in 43.0% of the ECMO group, compared to 7.0% of the standard ACLS group (posterior probability = 0.9861). The secondary outcome, survival to 6 months, occurred in 43.0% of the ECMO group, compared to 0.0% of the standard ACLS group ($p = 0.0063$). The ARREST trial showed that early implementation of ECMO was superior to standard ACLS at improving survival of people who suffered refractory VF/VT OHCA.[74] This trial paves the way for further research into advanced targeted therapies and advanced cardiac care.

Conclusions

VA-ECMO used as ECPR is a contemporary resuscitation approach that is likely associated with improved long-term neurologically intact survival after adult cardiac arrest. Using GRADE methodology we conclude that the quality of evidence is very low. We further conclude that evidence from randomized trials is very likely to have an important impact on the estimated effect of this intervention and will further define optimal clinical practice.

Author contributions

DM, LM, and WA were responsible for the study conception and design. DM and LM were responsible for data abstraction, analysis, and interpretation of the data. DM performed the statistical analysis and drafted the original manuscript. All authors reviewed and approved the final version of the manuscript. All authors meet ICMJE authorship criteria. DM takes responsibility for the integrity of the data, the accuracy of the data analysis and for the paper as a whole.

Declaration of competing interest

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resplu.2020.100045.

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