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# 1 Extracorporeal Cardiopulmonary Resuscitation for Cardiac Arrest: A 2 Systematic Review

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39 **ABSTRACT**

40 *Aim*

41 To assess the use of extracorporeal cardiopulmonary resuscitation (ECPR), compared with manual or mechanical  
42 cardiopulmonary resuscitation (CPR), for out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA)  
43 in adults and children.

44

45 *Methods*

46 The PRISMA guidelines were followed. We searched Medline, Embase, and Evidence-Based Medicine Reviews for  
47 randomized clinical trials and observational studies published before May 22, 2018. The population included adult  
48 and pediatric patients with OHCA and IHCA of any origin. Two investigators reviewed studies for relevance,  
49 extracted data, and assessed the quality of studies using the ROBINS-I tool. Outcomes included short-term and  
50 long-term survival and favorable neurological outcome.

51

52 *Results*

53 We included 25 observational studies, of which 15 studies were in adult OHCA, 7 studies were in adult IHCA, and 3  
54 studies were in pediatric IHCA. There were no studies in pediatric OHCA. No randomized trials were included.

55 Results from individual studies were largely inconsistent, although several studies in adult and pediatric IHCA were  
56 in favor of ECPR. The risk of bias for individual studies was overall assessed to be critical, with confounding being  
57 the primary source of bias. The overall quality of evidence was assessed to be very low. Heterogeneity across  
58 studies precluded any meaningful meta-analyses.

59

60 *Conclusions*

61 There is inconclusive evidence to either support or refute the use of ECPR for OHCA and IHCA in adults and  
62 children. The quality of evidence across studies is very low.

63

64 **INTRODUCTION**

65 Extracorporeal cardiopulmonary resuscitation (ECPR) is an advanced rescue therapy, where an extracorporeal  
66 circuit is employed, to support circulation in patients with cardiac arrest refractory to conventional CPR.[1] ECPR  
67 maintains vital organ perfusion while potential reversible causes of the cardiac arrest can be identified and  
68 treated.

69 ECPR is recognized by the American Heart Association (AHA)[2, 3] and the European Resuscitation Council  
70 (ERC)[4, 5] as a therapy which can be considered in select cardiac arrest patients, when rapid expert deployment is  
71 possible. However, the benefits of applying ECPR are not clear and optimal patient selection and timing of the  
72 therapy are not well-understood.[6] Furthermore, the ethical considerations related to using and studying ECPR  
73 are complex.[7] Given the recent increase in the availability and usage of ECPR for cardiac arrest[8-10], there is a  
74 need for a review of the evidence to guide the international consensus on ECPR in cardiac arrest.

75 The objective of this systematic review was to inform the update of the International Liaison Committee on  
76 Resuscitation (ILCOR) treatment recommendations by assessing the use of ECPR, compared to manual or  
77 mechanical cardiopulmonary resuscitation (CPR), for OHCA and IHCA of all causes in adults and children.

78  
79 **METHODS**

80 *Protocol and registration*

81 This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses  
82 (PRISMA) guidelines.[11] The PRISMA checklist is provided in the Supplementary Contents. The protocol and  
83 amendments were prospectively submitted to the International Prospective Register of Systematic Reviews  
84 (PROSPERO) (CRD42018085404). The protocol is provided in the Supplementary Contents. The review was  
85 commissioned by ILCOR.

86  
87 *Eligibility criteria*

88 We used the PICO (Population, Intervention, Comparison, Outcome) format to frame the study question: Among  
89 adults ( $\geq 18$  years) and children ( $< 18$  years) with cardiac arrest in any setting (out-of-hospital or in-hospital) (P),  
90 does the use of ECPR, including extracorporeal membrane oxygenation or cardiopulmonary bypass, during cardiac  
91 arrest (I), compared to manual CPR and/or mechanical CPR (C), change survival at hospital discharge, long-term  
92 survival, neurological outcome at discharge, and/or long-term neurological outcome (O).

93 Outcomes with similar time frames (i.e. short-term [hospital discharge, 28-days, 30-days, and 1-month] and  
94 long-term [3-months, 6-months, and 1-year]) were combined into single categories. Long-term survival reported as  
95 hazard ratios (i.e. survival analysis), irrespective of length of follow-up, was also considered. Return of  
96 spontaneous circulation (ROSC) was not included as an outcome since it is difficult to meaningfully define in this  
97 patient population.

98 Randomized trials, non-randomized controlled trials, and observational studies (cohort studies and case-  
99 control studies) with a control group (i.e. patients not receiving ECPR) were included. Animal studies, ecological  
100 studies, case series, case reports, reviews, abstracts, editorials, comments, and letters to the editor were not  
101 included. There were no limitations on publication period or study language. The population included patients with  
102 IHCA or OHCA of any origin, without age restriction. Studies with  $\leq 5$  patients receiving ECPR or studies that did not  
103 report timing of ECPR (i.e. not clear whether ECPR was used during or after cardiac arrest) were excluded.

104 Studies exclusively assessing the use of extracorporeal life support for cardiac and/or respiratory failure after  
105 sustained ROSC were not included. Studies reporting the use of extracorporeal circulation for accidental  
106 hypothermia, pulmonary embolism, overdoses, or other conditions were included if cardiac arrest was  
107 documented. Studies assessing cost-effectiveness of ECPR were considered for a descriptive summary.

108

#### 109 *Information sources and search strategy*

110 We searched the following electronic bibliographic databases on December 19, 2017: Medline, Embase, and  
111 Evidence-Based Medicine Reviews (which includes the Cochrane Library). The search was repeated on May 22,  
112 2018 to capture any articles published during the review process. We used a combination of various search terms  
113 for *cardiac arrest* and *extracorporeal circulation*. The bibliographies of included articles were reviewed for  
114 potential additional articles. To identify ongoing trials, we searched the International Clinical Trials Registry  
115 Platform (<http://www.who.int/ictpr/en/>) (which includes entries in ClinicalTrials.gov) on March 13, 2018. The  
116 search strategies for each database and the Clinical Trials Registry Platform are provided in eTable 1–2 in the  
117 Supplementary Contents.

118

#### 119 *Study selection*

120 Two reviewers, using pre-defined screening criteria, independently screened all titles and abstracts retrieved from  
121 the systematic review. The reviewers were blinded to authors and journal titles during the screening stage. Any  
122 disagreement regarding inclusion or exclusion were resolved via discussion between the reviewers and with a third  
123 reviewer as needed. The Kappa-value for inter-observer variance was calculated. In case of only weak or moderate  
124 agreement between reviewers (i.e. a Kappa  $< 0.80$ [12]) a third reviewer reviewed all excluded titles and abstracts  
125 to ensure optimized sensitivity. Two reviewers then reviewed the full text-reports of all potentially relevant  
126 publications passing the first level of screening. Any disagreement regarding eligibility was resolved via discussion.

127

#### 128 *Data collection and data items*

129 Two reviewers using a pre-defined standardized data extraction form extracted data as pertinent to the PICO (see  
130 “Eligibility criteria”). Missing statistical parameters (i.e. odds ratios) of importance and variance measures (i.e.  
131 confidence intervals) were calculated if data permitted. Any discrepancies in the extracted data were identified  
132 and resolved with discussion and consensus.

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*Risk of bias in individual studies*

Two investigators independently assessed risk of bias for the included studies. Risk of bias was assessed by the ROBINS-I tool[13] for observational studies. In the ROBINS-I tool, risk of bias is assessed within specified domains, including (1) bias due to confounding, (2) bias in selection of participants into the study, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions (5) bias due to missing data, (6) bias in measurement of outcomes, (7) bias in selection of the reported result, and (8) overall bias.[13] Bias assessments were tabulated with explanations when studies were downgraded. Since assessments are inherently subjective and there are no strict and objective criteria to judge bias within the ROBINS-I tool[13], disagreements were resolved via discussion between the two investigators. Bias was assessed per study rather than per outcome, since there were no meaningful differences in bias across outcomes.

*Data synthesis and confidence in cumulative evidence*

Studies were assessed for clinical (i.e. participants, interventions, and outcomes), methodological (i.e. study design or risk of bias), and statistical heterogeneity.[14] Separate meta-analyses were planned for adult IHCA, adult OHCA, pediatric IHCA, and pediatric OHCA as described in the protocol.

The quality of the overall evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology ranging from very low quality of evidence to high quality of evidence.[15] Detailed assessment of overall risk of bias, inconsistency, indirectness, imprecision and potential other issues such as publication bias were tabulated.

Review Manager (The Cochrane Collaboration, 2014) was used to generate forest plots.

**RESULTS**

*Study selection*

The search strategy identified 7,458 records of which 74 records were eligible for full-text review. The Kappa for identifying records during the initial screening of the first search was 0.38 prompting review by a third reviewer. A PRISMA diagram of the study selection process is presented in Figure 1. No randomized clinical trials were identified. Twenty-five observational studies met all of the inclusion criteria and none of the exclusion criteria.[16-40] Fifteen studies were in adult OHCA[16-30], 7 studies were in adult IHCA[31-37], and 3 studies were in pediatric IHCA[38-40]. We identified no studies in pediatric OHCA. An overview of each included study is provided in Table 1–3 and details are provided in the Supplementary Contents. We identified 5 ongoing clinical trials in adult OHCA on the International Clinical Trials Registry Platform. An overview of each trial is provided in Table 4. We did not identify any studies assessing the cost-effectiveness of ECPR in cardiac arrest.

*Adult out-of-hospital cardiac arrest*

168 Fifteen of the included studies were in adult OHCA.[16-30] Eight studies were performed in Asia[18-22, 24, 26, 27],  
169 4 studies in Europe[16, 17, 23, 25], and 3 studies in North America[28-30]. Three studies included both OHCA and  
170 IHCA patients.[17, 21, 28] The cohort and/or time-frame was overlapping for some studies.[19, 22, 27, 29, 30]  
171 Years of patient inclusion ranged from 1999 to 2015. The majority of studies defined the exposure as “ECPR use”,  
172 whereas one study[24] defined the exposure as “ECPR availability” and two studies[29, 30] defined exposure as a  
173 “ECPR strategy”. The median age of exposed patients ranged from 46 to 59 years. Twelve studies reported survival  
174 to hospital discharge, 6 studies reported long-term survival, 8 studies reported favorable neurological outcome at  
175 hospital discharge, and 6 studies reported long-term favorable neurological outcomes. All studies defined  
176 favorable neurological outcome as a Cerebral Performance Category score of 1–2. Forests plots of each outcome  
177 are presented in Figure 2. Additional details for each individual study are provided in Table 1 and the  
178 Supplementary Contents.

179

#### 180 *Adult in-hospital cardiac arrest*

181 Seven of the included studies were in adult IHCA.[31-37] Six studies were performed in Asia[32-37] and one study  
182 was performed in Europe[31]. The cohort and/or time-frame was overlapping for some studies.[32, 33, 35-37]  
183 Years of patient inclusion ranged from 2001 to 2013. The majority of studies defined the exposure as “ECPR use”,  
184 whereas two studies[36, 37] defined the exposure as “ECPR attempt”. The median age of exposed patients ranged  
185 from 57 to 72 years. Six studies reported survival to hospital discharge, 6 studies reported long-term survival, 5  
186 studies reported favorable neurological outcome at hospital discharge, and 5 studies reported long-term favorable  
187 neurological outcome. Four studies reported survival analyses with length of follow-up ranging from 1 to 3 years.  
188 All studies defined favorable neurological outcome as a Cerebral Performance Category score of 1–2. Forests plots  
189 of each outcome are presented in Figure 3. Additional details for each individual study are provided in Table 2 and  
190 the Supplementary Contents.

191

#### 192 *Pediatric in-hospital cardiac arrest*

193 Three of the included studies were in pediatric IHCA.[38-40] All studies were performed in North America, of which  
194 two studies[38, 40] were from the Get With The Guidelines® registry. Years of patient inclusion ranged from 2000  
195 to 2011. All studies defined the exposure as “ECPR use”. All studies reported survival to hospital discharge,  
196 whereas only one study reported favorable neurological outcome at hospital discharge. Favorable neurological  
197 outcome was defined as a Pediatric Cerebral Performance Category score of 1–3. Forests plots of each outcome  
198 are presented in Figure 4. Additional details for each individual study are provided in Table 3 and the  
199 Supplementary Contents.

200

#### 201 *Risk of bias for individual studies*



202 The risk of bias within individual studies was judged overall as critical for all studies, with confounding being the  
203 primary source. Risk of selection bias was judged to be low for the majority of studies. Few studies were at  
204 moderate risk of bias for missing data. The majority of studies did not report any missing data and were therefore  
205 classified as low risk of bias, but the risk of bias could also be considered “unknown”. All studies were at moderate  
206 risk for selective reporting since none provided a pre-registered protocol. The remaining ROBINS-I domains were  
207 all judged to be at low risk of bias. A detailed list of risk of bias assessments is provided in eTable 3 in the  
208 Supplementary Contents.

209

#### 210 *Quality of evidence across studies*

211 The overall quality of evidence across all studies were judged to be of very low quality. GRADE summary tables and  
212 additional details are provided in eTable 4–6 in the Supplementary Contents.

213

#### 214 *Meta-analyses, meta-regression, and publication bias*

215 The critical risk of bias and heterogeneity between studies did not allow for any meaningful meta-analyses. We  
216 were not able to conduct meta-regression or test for publication bias because too few studies were identified.

217

### 218 **DISCUSSION**

219 In this systematic review, we identified studies comparing the use of ECPR to manual or mechanical CPR for OHCA  
220 and IHCA in adult and pediatric patients. We identified 25 observational studies, of which 15 studies were in adult  
221 OHCA, 7 studies were in adult IHCA, and 3 studies were in pediatric IHCA. No randomized clinical trials were  
222 identified, though several are ongoing as noted on the International Clinical Trials Registry Platform. Results from  
223 studies in OHCA were inconsistent. Studies in adult and pediatric IHCA were generally in favor of ECPR, although  
224 the risk of bias for individual studies was overall assessed to be critical. The quality of evidence was very low across  
225 all outcomes.

226 The goal of ECPR is to support patients with cardiac arrest by providing time for recovery, diagnostics, and/or  
227 treatment of potentially reversible causes. The use of ECPR is complex and requires local expertise, specialized  
228 equipment, rigorous patient selection, and careful timing.[2, 3, 6] The location of cardiac arrest is of particular  
229 relevance in this context, since patients who experience OHCA are significantly different from patients who  
230 experience IHCA.[41-44] Patients with IHCA tend to have shorter low-flow time and are more likely to have rapid  
231 access to a dedicated ECPR response team. While the use of in-hospital extracorporeal life support has increased  
232 over the past decade[8-10], ECPR is not readily available for pre-hospital use and patients who experience OHCA  
233 are reliant on rapid transportation to ECPR capable hospitals[45].

234 The included studies were all assessed to have a critical risk of confounding potentially limiting internal  
235 validity. First, the final decision to perform ECPR is generally made on a case-by-case basis, which may limit the  
236 comparability between those receiving ECPR following a period of CPR and those with no ECPR. The factors driving

237 the decision to use ECPR are based on clinical assessments of the underlying disease, the assumption that  
238 conventional CPR will not be effective, and boundaries set by deployment protocols. These factors may be related  
239 to outcomes and could therefore bias the results. Second, many studies only reported unadjusted results[16-19,  
240 23-25, 27-30, 34, 39] or did not adjust adequately for important confounders. For instance, very few studies  
241 accounted for pre-cardiac arrest performance status or activities of daily living[22] and none of the studies  
242 adjusted for intra-cardiac arrest variables (e.g., end-tidal CO<sub>2</sub>, lactate, pH, potassium). In addition, studies  
243 accounting for past-medical history[21, 31, 32, 35-38], used crude measurements (e.g., renal disease vs. no renal  
244 disease, cardiac disease vs. no cardiac disease), which increases the risk of residual confounding. Third, most  
245 studies adjusted for “CPR duration”.[20-22, 26, 31-33, 35-38, 40] This is problematic, since “CPR duration” could be  
246 a mediator on the causal pathway between ECPR and outcomes[46] and because “CPR duration” is defined  
247 differently for patients receiving ECPR (time to ECPR, which was rarely well-defined) and no ECPR (time to ROSC or  
248 death). Adjusting for “CPR duration” using traditional methods is therefore likely to introduce biased results,  
249 although the direction of this bias can be difficult to predict.[47] Some studies also adjusted for treatments after  
250 the cardiac arrest (e.g., targeted temperature management)[20, 22, 26, 36, 37], which may bias the results, since  
251 these variables cannot be direct confounders of the relationship between ECPR and outcomes.[47] These  
252 limitations illustrate the need for rigorous randomized clinical trials or alternative study designs minimizing bias to  
253 clarify the role of ECPR in cardiac arrest.

254 The vast majority of the included studies were single-center studies[17-22, 25-37, 39], with varying inclusion  
255 criteria and settings. Some studies in adult OHCA restricted their inclusion criteria to patients with a witnessed  
256 cardiac arrest, very short no-flow times, and/or required a certain duration of conventional CPR prior to ECPR.[17,  
257 18, 22, 25, 26] Three studies assessed the availability and/or use of ECPR in the cardiac catheterization  
258 laboratory.[28-30] The results of these studies are not easily applicable to other settings. Studies in adult and  
259 pediatric IHCA were less diverse, although one adult study restricted inclusion to patients with cardiac arrest  
260 caused by acute pulmonary embolism.[33] ECPR technology[1] and costs[48] may also have varied across studies  
261 and time. The high-degree of heterogeneity between studies limited our ability to perform meta-analyses and  
262 reduced the generalizability of the included studies.

263 While we report on the use of ECPR in relation to outcomes, we did not evaluate patient selection, indication,  
264 and prognostication related to ECPR. A recent position paper by Abrams et al. has highlighted some of these  
265 issues, proposing that ECPR may be initiated by rapid-response teams within 15 minutes of conventional CPR in  
266 patients without severe comorbidities[6], although there is little evidence to support such a recommendation.  
267 Systematic reviews in IHCA[49] and OHCA[50] recently assessed prognostic factors of favorable outcome in adult  
268 patients receiving ECPR. Both reviews found initial shockable rhythms, short low-flow time, and low lactate values  
269 at admission to be associated with better outcomes. In the context of resource utilization, we did not identify any  
270 cost-effectiveness studies for ECPR specific to cardiac arrest. One study reported hospital costs without performing  
271 a cost-effectiveness analysis[51] and two studies conducted cost-effectiveness analyses for ECPR primarily

272 including non-cardiac arrest patients[52, 53]. Understanding the clinical benefits of ECPR relative to the resource  
273 utilization is particularly important given the recent increased use of ECPR.

274

275 **CONCLUSIONS**

276 There is inconclusive evidence to either support or refute the use of ECPR for OHCA and IHCA in adults and  
277 children. The quality of evidence across studies is very low. Future investigations should be cautious of issues  
278 related to internal validity. Randomized clinical trials are needed to better inform clinical practice.

279 **CONFLICTS OF INTEREST**

280 None of the authors have any conflicts of interest to report. Dr. Andersen was compensated by ILCOR for his work  
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289

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301

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450

451 **FIGURE LEGENDS**

452

453 **Figure 1. PRISMA diagram**

454 Out of 7458 screened records, 74 articles were assessed for eligibility, and 25 studies were included.

455

456 **Figure 2. Forest plots for adult out-of-hospital cardiac arrest**

457 Forest plots for survival to hospital discharge/one month (A), long-term survival (B), favorable neurological  
458 outcome at hospital discharge/one month (C), and long-term favorable neurological outcome (D) in adult out-of-  
459 hospital cardiac arrest. The vertical red lines indicate odds ratios. Horizontal lines indicate 95% confidence intervals  
460 of the estimate. The studies are ordered by alphabetical order within each outcome. The forest plots for long-term  
461 outcomes are representative of all included patients, independent of survival to hospital discharge. The studies by  
462 Cesana et al. (2017), Lee et al. (2015), and Venturini et al. (2017) include both out-of-hospital cardiac arrest and in-  
463 hospital cardiac arrest patients. There was some overlap between the studies by Hase (2005), Maekawa (2013) and  
464 Tanno (2008), and between Yannopolous (2016+2017).

465 *OHCA refers to out-of-hospital cardiac arrest.*

466

467 **Figure 3. Forest plots for adult in-hospital cardiac arrest**

468 Forest plots for survival to hospital discharge/one month (A), long-term survival (B), favorable neurological  
469 outcome at hospital discharge/one month (C), long-term favorable neurological outcome (D), and survival analysis  
470 (E) in adult in-hospital cardiac arrest. The vertical red lines indicate odds ratios or hazard ratios. Horizontal lines  
471 indicate 95% confidence intervals of the estimate. For the survival analysis (hazard ratios from Cox proportional  
472 hazard models) with time-to-death as the outcome, estimates below 1 are in favor of ECPR. The studies are  
473 ordered by alphabetical order within each outcome. The forest plots for long-term outcomes are representative of  
474 all included patients, independent of survival to hospital discharge. There was some overlap between the studies  
475 by Chen (2008) and Lin (2010), and between Cho (2014) and Shin (2011+2013).

476 *IHCA refers to in-hospital cardiac arrest.*

477

478 **Figure 4. Forest plots for pediatric in-hospital cardiac arrest**

479 Forest plots for survival to hospital discharge (A) and favorable neurological outcome at hospital discharge (B) in  
480 pediatric in-hospital cardiac arrest. The vertical red lines indicate odds ratios. Horizontal lines indicate 95%  
481 confidence intervals of the estimate. The studies are ordered by alphabetical order within each outcome. The 95%  
482 confidence interval reported by Ortmann et al. (medical-group) was non-symmetric and therefore re-estimated.  
483 There was some overlap between the studies by Lasa (2016) and Ortmann (2011).

484 *IHCA refers to in-hospital cardiac arrest.*

485

486

Table 1. Characteristics of studies in adult out-of-hospital cardiac arrest <sup>a,b</sup>					
Study	Country	Years of inclusion	Inclusion criteria	Exclusion criteria	Patients analyzed (n)
Agostinucci, 2011[16]	France	2005 – 2010	Use of load-distributing band	Not Reported	285
Cesana, 2017[17]	Italy	2011 – 2015	Age 18-75 years, witnessed, ischemic etiology, absence of comorbidities precluding ICU admission	Not Reported	148
Choi, 2016[18]	Korea	2011 – 2015	Non-traumatic, age ≤ 75, witnessed, bystander CPR or no-flow time ≤ 5 min, prehospital low-flow time ≤ 30 min and > 10 min of conventional CPR at ED, absence of severe comorbidities	DNR, poor performance status or terminal illness, trauma, intracranial hemorrhage, acute aortic dissection, ROSC within 10 min of ED arrival	60
Hase, 2005[19]	Japan	1999 – 2003	Cardiac etiology	Not Reported	100
Kim, 2014[20]	Korea	2006 – 2013	Age > 18 years, non-traumatic	Not Reported	104
Lee, 2015[21]	Korea	2009 – 2014	Not Reported	Not Reported	955
Maekawa, 2013[22]	Japan	2000 – 2004	Cardiac etiology, age > 16 years, witnessed, CPR duration > 20 min	DNR, dead prior to hospital arrival	48
Poppe, 2015[23]	Austria	2003 – 2014	Age > 18 years, ongoing CPR	Not Reported	96
Sakamoto, 2014[24]	Japan	2008 – 2011	Shockable rhythm, cardiac arrest on arrival, 45 min from cardiac arrest onset to hospital arrival, no ROSC within 15 min after hospital arrival	Age < 20 or > 75 years, poor level of activities of daily living, non-cardiac etiology, body temperature < 30 C, no informed consent	454
Schober, 2017[25]	Austria	2002 – 2012	Cardiac origin, CPR duration > 30 min	Clinical indication for E-CPR	239
Siao, 2015[26]	Taiwan	2011 – 2013	Age 18-75 years, ventricular fibrillation, no-flow time < 5 min, refractory cardiac arrest	Head trauma or active bleeding, severe sepsis, initial non-shockable rhythm, terminal malignancy, history	60

Tanno, 2008[27]	Japan	2000 – 2004	Age > 16 years, cardiac etiology	of neurological deficits Not Reported	398
Venturini, 2017[28]	USA	2011 – 2016	CPR in cardiac catheterization laboratory, mechanical chest compressions	Not Reported	31
Yannopoulos, 2016[29]	USA	2015 – 2016	Age 18-75 years, cardiac etiology, shockable rhythm, 3 direct current shocks, amiodarone, eligible mechanical CPR, time to CCL < 30 minutes	Nursing home resident, DNR, known terminal illness, significant bleeding	188
Yannopoulos, 2017[30]	USA	2015 – 2016	Age 18-75 years, cardiac etiology, shockable rhythm, 3 direct current shocks, amiodarone, eligible mechanical CPR, transfer time from scene to CCL < 30 minutes	Nursing home resident, DNR, known terminal illness, significant bleeding	232

488 E-CPR refers to extracorporeal cardiopulmonary resuscitation, CPR refers to cardiopulmonary resuscitation, ED  
489 refers to emergency department, ICU refers to intensive care unit, DNR refers to do-not-resuscitate, ROSC refers to  
490 return of spontaneous circulation; CCL refers to cardiac catheterization laboratory.  
491 <sup>a</sup> All studies compared ECPR vs. no ECPR whereas Sakamoto (2014) compared emergency departments with ECPR  
492 vs. emergency departments with no ECPR.  
493 <sup>b</sup> There was some overlap between the studies by Hase (2005), Maekawa (2013) and Tanno (2008), and between  
494 Yannopoulos (2016+2017).

<b>Study</b>	<b>Country</b>	<b>Years of inclusion</b>	<b>Inclusion criteria</b>	<b>Exclusion criteria</b>	<b>Patients analyzed (n)</b>
Blumenstein, 2015[31]	Germany	2009 – 2013	Cardiovascular admission, witnessed	Not Reported	353
Chen, 2008[32]	Taiwan	2004 – 2006	Age 18-75 years, CPR duration > 10 min, cardiac etiology, witnessed	Previous irreversible brain damage, terminal malignancy, DNR	92
Cho, 2014[33]	Korea	2001 – 2013	Pulmonary embolism	Non-survivors of CPR	20
Chou, 2013[34]	Taiwan	2006 – 2010	Age > 18 years, acute myocardial infarction, CPR > 10 min	Terminal malignancy, previously irreversible brain damage, DNR, ROSC within 10 min	66
Lin, 2010[35]	Taiwan	2004 – 2006	Age 18-75 years, cardiac etiology, CPR duration > 10 min, ROSC	Not Reported	54
Shin, 2011+2013[36, 37]	Korea	2003 – 2009	Age 18-80 years, CPR duration > 10 min, witnessed	Previous neurologic damage, intracranial hemorrhage, terminal malignancy, traumatic origin with bleeding, septic origin, organ failure despite maximal therapy, DNR	120

495 E-CPR refers to extracorporeal cardiopulmonary resuscitation, CPR refers to cardiopulmonary resuscitation, DNR  
496 refers to do-not-resuscitate, ROSC refers to return of spontaneous circulation.

497 <sup>a</sup> All studies compared ECPR vs. no ECPR whereas Shin et al. compared ECPR attempt vs. no ECPR attempt.

498 <sup>b</sup> There was some overlap between the studies by Chen (2008) and Lin (2010), and between Cho (2014) and Shin  
499 (2011+2013).

500 <sup>b</sup> The studies by Shin (2011+2013) included the same patient population, but reported different outcomes.

**Table 3. Characteristics of studies in pediatric in-hospital cardiac arrest<sup>a</sup>**

Study	Country	Years of inclusion	Inclusion criteria	Exclusion criteria	Patients analyzed (n)
Lasa, 2016[38]	USA	2000 – 2011	Age < 18 years, CPR duration ≥ 10 min	Hospitals with no E-CPR cases, events in the delivery room or rehabilitation facility or same-day surgery center, obstetric and traumatic events	3,756
Odegard, 2014[39]	USA	2004 – 2009	Cardiac arrest during cardiac catheterization	Not Reported	70
Ortmann, 2011[40]	USA	2000 – 2008	Age < 18 years, cardiac admission	Not Reported	Medical: 574 Surgical: 640

501 E-CPR refers to extracorporeal cardiopulmonary resuscitation, CPR refers to cardiopulmonary resuscitation.

502 <sup>a</sup> There was some overlap between the studies by Lasa (2016) and Ortmann (2011).

**Table 4. Overview of ongoing randomized clinical trials registered online**

Title	ID <sup>a</sup>	Country	Estimated Completion Date	Objective	Patients (n)
Hyperinvasive Approach in Cardiac Arrest	NCT01511666	Czech Republic	May 2018	Determine the advantage of prehospital intra-arrest hypothermia, mechanical CPR, ECLS, and early invasive assessment vs. standard of care.	170
Emergency Cardiopulmonary Bypass for Cardiac Arrest	NCT01605409	Austria	May 2018	Determine the feasibility of ECPB installed in an ED vs. standard of care	40
ECPR for Refractory Out-Of-Hospital Cardiac Arrest	NCT03065647	USA	December 2018	Determine the feasibility of expedited transport to an ED capable of initiating ECPR vs. standard of care	30
A Comparative Study Between a Pre-hospital and an In-hospital Circulatory Support Strategy in Refractory Cardiac Arrest	NCT02527031	France	March 2019	Determine the advantage of pre-hospital ECMO vs. in-hospital ECMO	210
Early Initiation of Extracorporeal Life Support in Refractory OHCA	NCT03101787	Netherlands	May 2019	Determine the effect of ECPR in ED vs. standard of care	110

503 OHCA refers to out-of-hospital cardiac arrest, ROSC refers to return of spontaneous circulation, ECPB refers to  
504 emergency cardiopulmonary bypass, ECPR refers to extracorporeal cardiopulmonary resuscitation, ECMO refers to  
505 extracorporeal membrane oxygenation, CCPR refers to conventional cardiopulmonary resuscitation, ED refers to  
506 emergency department, CPR refers to cardiopulmonary resuscitation, ECLS refers to extracorporeal life support

507 <sup>a</sup> All studies were registered at [clinicaltrials.gov](http://clinicaltrials.gov)  
508