



## Review article

# Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: A systematic review of international practices and outcomes<sup>☆</sup>



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## ABSTRACT

**Aim:** Extracorporeal resuscitation during cardiopulmonary resuscitation (ECPR) deploys rapid cardiopulmonary bypass to sustain oxygenated circulation until the return of spontaneous circulation (ROSC). The purpose of this systematic review is to address the defining elements and outcomes (quality survival and organ donation) of currently active protocols for ECPR in refractory out-of-hospital cardiac arrest (OHCA) of cardiac origin in adult patients. The results may inform policy and practices for ECPR and help clarify the corresponding intersection with deceased organ donation.

**Methods:** We searched Medline, Embase, Cochrane and seven other electronic databases from 2005 to 2015, with no language restrictions. Internal validity and the quality of the studies reporting outcomes and guidelines were assessed. The review was included in the international prospective register of systematic reviews (Prospero, CRD42014015259).

**Results:** One guideline and 20 outcome studies were analyzed. Half of the studies were prospective observational studies assessed to be of *fair to good* methodological quality. The remainder were retrospective cohorts, case series, and case studies. Ages ranged from 16 to 75 years and initial *shockable* cardiac rhythms, witnessed events, and a reversible primary cause of cardiac arrest were considered favorable prognostic factors. CPR duration and time to hospital cannulation varied considerably. Coronary revascularization, hemodynamic interventions and targeted temperature management neuroprotection were variable. A total of 833 patients receiving this ECPR approach had an overall reported survival rate of

**Abbreviations:** ECPR, extracorporeal resuscitation; ROSC, return of spontaneous circulation; OHCA, out-of-hospital cardiac arrest; CPC, cerebral performance category; GOS, Glasgow Outcome Scale; LOE, level of evidence; ILCOR, International Liaison Committee on Resuscitation; RCTs, randomized controlled trials; TTM, targeted temperature management; IABP, intra-aortic balloon pump; DBD, donation after brain death; cDCD, controlled donation after circulatory determination of death; ELSO, extracorporeal life support organization.

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22%, including 13% with good neurological recovery. Additionally, 88 potential and 17 actual deceased organ donors were identified among the non-survivor population in 8 out of 20 included studies. Study heterogeneity precluded a meta-analysis preventing any meaningful comparison between protocols, interventions and outcomes.

**Conclusions:** ECPR is feasible for refractory OHCA of cardiac origin in adult patients. It may enable neurologically good survival in selected patients, who practically have no other alternative in order to save their lives with quality of life, and contribute to organ donation in those who die. Large, prospective studies are required to clarify patient selection, modifiable outcome variables, risk-benefit and cost-effectiveness.

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## Introduction

Sudden cardiac arrest is the main cause of death worldwide in previously healthy people. The global incidence of OHCA in adults is 62 cases per 100,000 persons per year, from which 75 to 85% have a cardiac origin.<sup>1</sup> Despite recent improvements in enhancing successful resuscitation in the prehospital setting, overall outcomes remain poor in most venues.<sup>1</sup> The overall reported survival to hospital discharge is 6% in North America,<sup>1</sup> 9% in Europe, 11% in Australia and 2% in Japan.<sup>2</sup>

Extracorporeal resuscitation deploys a modified form of cardiopulmonary bypass, maintaining circulation until an effective cardiac output can be restored. This technique enhances coronary blood flow and preserves the heart's viability, increasing the chance of ROSC. The supply of oxygenated blood flow to the body and brain prevents organ dysfunction and increases the likelihood of survival with a good neurological recovery.<sup>3</sup> It is referred to as ECPR for patients in cardiac arrest when conventional resuscitation attempts fail, and it provides oxygenated circulation to extend the time window to diagnose and treat the underlying primary cause of the arrest. In recent years, ECPR has been proposed as an effective therapy not only for in-hospital cardiac arrest, but also for OHCA.<sup>4,5</sup> However, the results have been mixed due to heterogeneity in study populations, interventions and patient follow-up. In OHCA events, adult patients are known to be younger, previously healthy and the cause of cardiac arrest is more likely of cardiac origin. Therefore, these sudden death episodes are potentially more reversible than in patients who suffer an in-hospital cardiac arrest associated with many comorbidities. Given ROSC is not achieved in the majority of refractory OHCA<sup>1,2</sup> the ECPR strategy may be a final option for these selected patients "too healthy to die".<sup>6</sup>

The purpose of this systematic review is to address the defining elements and outcomes (quality survival and organ donation) of currently active protocols for ECPR in refractory OHCA of cardiac origin in adult patients. Further understanding of survival outcomes versus risks of anoxic brain injury and death may inform policy and practices for ECPR and the corresponding intersection with deceased organ donation and transplantation.

## Methods

### Design of the study and search strategy

A systematic review of the literature was conducted according to health care reviews from the University of York's Center for Reviews and Dissemination.<sup>7</sup>

Medline (OvidSP), Embase (OvidSP), Cochrane (Wiley) and seven other electronic databases were searched by an expert librarian (EG) from January 1st, 2005 to May 25, 2015 with no language restrictions. Articles identified included variations of the terms ECPR or extracorporeal circulation, found as textwords in the Title/Abstract or MeSH. These were combined with variations of resuscitation, out of hospital, in hospital, cardiac and

organ donation terms found in the Title/Abstract or MeSH. We also searched Google Scholar, clinicaltrials.gov, as well as reference lists of included studies, abstracts, unpublished reports, personal libraries (IO-D), professional organization reports and government agency statements on ECPR. Two reviewers (IO-D & LH) extracted main variables. Internal validity and the quality of the studies reporting outcomes and guidelines were assessed. The review was included in the international prospective register of systematic reviews (Prospero, CRD42014015259) (see Additional file 1 for search strategy details).

We used a modified PICOTS format. **Population:** adults with refractory OHCA of cardiac origin, who were considered candidates for ECPR; **Intervention:** ongoing resuscitation during transport, followed by ECPR and other adjunctive therapies until and/or early after ROSC; **Control:** although most of the selected studies are single-arm studies, conventional resuscitation was compared to the ECPR strategy in applicable studies; **Outcomes:** description of practices based on ECPR protocols applied to the population, survival with quality of life according to a cerebral performance category (CPC) score 1–2 or Glasgow Outcome Scale (GOS) score 4–5 at discharge, and potential organ donation; **Time:** from January 2005 to May 2015; **Setting:** organizations that produced recommendations or conducted studies consistent with our eligibility criteria.

### Eligibility criteria

Studies reporting results from ECPR in adult patients with refractory OHCA of cardiac origin and recommendations for ECPR endorsed by any professional society or health care authority were included. We excluded editorials, reviews, abstracts, letters or personal opinions. Human studies that included patients with cardiac arrest of non-cardiac origin (e.g. trauma, massive bleeding, hypothermia, poisoning, near drowning, etc.) and animal studies were also excluded. Two trained reviewers (IO-D & LH) selected the studies and screened citations, retrieved the full texts and independently reviewed them to assess study eligibility. Disagreements were resolved by consensus or after input of two other expert reviewers (SDS & FB). We used EndNote manager software (End-Note X7.1 version, by Thomson Reuters) to manage the collection of publications. Fig. 1 presents the flow chart study selection process (PRISMA).

### Data extraction and quality assessment

Two reviewers (IO-D and LH) extracted data after creating an Excel (Excel version 2013, by Microsoft Office) data collection tool that was piloted in a sample from included studies. The spreadsheet tabulated the following variables: authors, country, setting, year of protocol, methodology, eligibility criteria, number of cases, interventions, timelines, results (survival with quality of life and potential/actual deceased donors) and conclusions.

The internal validity of the studies was assessed (See Table 1) independently by four reviewers (IO-D, LH, SDS & FB) and guideline

**Table 1**  
Characteristics and outcomes of included studies.

Study country, region	Study design	Time period	LOE (quality)	Sample size	Age <sup>a</sup> (years) male %	Cardiac rhythm no. (%)	No flow <sup>b</sup> period (min)	Low flow <sup>b</sup> period (min)	Survival at discharge (or as indicated) no. (%)	Neurological outcome at discharge (or as indicated) no. (%)	Organ donor no. (potential/actual)
Shin et al. <sup>17</sup> Korea, Seoul	Case report	2006	4 (fair)	1	37 (100)	1 (100) VF	0	approx 120	1 (100)	1 (100) CPC-1	NA
Nagao et al. <sup>15,c</sup> Japan, Tokyo	Prospective observational	November 2000 December 2007	4 (good)	171	MR	143 (84) VF/VT 18 (10) PEA 10 (6) AS	MR	MR	33(19)	21 (12) CPC-1,2	NR
Lebreton et al. <sup>21</sup> France, Paris	Case report	2010	4 (fair)	1	48 (100)	1 (100) AS	<1	<59	0 (0)	NA	NR
Le Guen et al. <sup>20,c</sup> France, Paris	Prospective observational	January 2008 August 2010	4 (good)	51	42 (90)	32 (63) VF 15 (29) AS 4 (8) PEA	3	NR	2 (4) <b>at 28 d</b>	2 (4) GOS 4,5 <b>at 6 months</b>	NR
Megarbane et al. <sup>22</sup> France, Paris	Prospective observational	2005–2008	4 (good)	47	MR	MR	MR	MR	1 (2)	1 (2) CPC-1	NR
Avalli et al. <sup>26,c</sup> Italy, Monza	Retrospective database review	January 2006 February 2011	4 (good)	18	46 (94)	16 (89) VF/VT 2 (11) AS/PEA	1	77	1 (5) <b>at 28 d</b>	1 (5) GOS ≥4 <b>at 6 months</b>	10 DBD/NR
Haneya et al. <sup>24,c</sup> Germany, Resenburger	Retrospective database review	January 2007 January 2012	4 (good)	26	48 (65)	12 (46) VF/VT 2 (8) PEA 12 (46) AS	NR	70 (55–110)	4 (15)	NR for OHCA alone	NR
Shinar et al. <sup>30</sup> US/San Diego	Case report	2011	4 (fair)	1	59 (100)	1 (100) VF	0	61	1 (100)	1 (100) CPC-1	NA
Fagnoul et al. <sup>28,g</sup> Belgium, Brussels	Prospective observational	January 2012 December 2012	4 (good)	7	MR	MR	MR	MR	2 (29)	2 (29) CPC-1	3 DBD, 1 DCD/1 DBD, 1 DCD
Lamhaut et al. <sup>19</sup> France, Paris	Pilot prospective observational	January 2011 January 2012	4 (fair)	7	42 (86)	5 (71) VF/VT	4 (mean)	72 (mean)	2 (28) <b>at 7 d</b>	1 (14%) CPC 1 <b>at 90 d</b>	3 DBD/2 DBD
Leick et al. <sup>25</sup> Germany, Bad Nauheim	Retrospective chart review	January 2010 December 2011	4 (good)	28	MR	MR	MR	MR	11 (39)	8 (29) CPC-1	NR
Maekawa et al. <sup>13</sup> Japan, Sapporo	Post hoc analysis of prospective observational	January 2000 September 2004	3 (good)	53	54 (83)	31(60) VF/VT	2	49	17 (32)	8 (15) CPC-1,2 <b>at 90 d</b>	44/0 <sup>d</sup>
Mojoli et al. <sup>27</sup> Italy, Pavia	Prospective observational	January 2008 June 2011	4 (fair)	7	55	NR	7	93 (no flow included)	0 (0)	NA	3 DBD, 1 DCD/2 DBD, 1 DCD
Tazarourte et al. <sup>23,f</sup> France, Ile de France region	Retrospective observational	2008–2010	4 (good)	27	39 (56)	VF 7 (26) PEA 6 (22) AS 14 (52)	2	140 (no flow included)	1 (4)	1 (4) CPC-1	10 DBD/10 DBD
Kim et al. <sup>12,c</sup> Korea, Seoul	Post hoc analysis of prospective observational	May 2006 December 2013	3 (good)	55	53 (75)	31 (56) VF/VT 14 (26) AS 10 (18) PEA	7	62	9 (16)	8 (15) CPC-1,2 1 (2) CPC-4	NR

Table 1 (Continued)

Study country, region	Study design	Time period	LOE (quality)	Sample size	Age <sup>a</sup> (years) male %	Cardiac rhythm no. (%)	No flow <sup>b</sup> period (min)	Low flow <sup>b</sup> period (min)	Survival at discharge (or as indicated) no. (%)	Neurological outcome at discharge (or as indicated) no. (%)	Organ donor no. (potential/actual)
Mochizuki et al. <sup>14</sup> Japan, Matsumoto	Retrospective database review	April 2004 March 2013	4 (good)	32	51 (78)	MR	MR	MR	8 (25) <b>at 30 d</b>	5 (16) CPC-1,2 <b>at 30 d</b>	5 DBD, 5DCD/0
Putzer et al. <sup>29</sup> Austria, Innsbruck	Case study	NR	4 (fair)	1	43 (100)	1 (100) VF	<5	107	1 (100)	1 CPC-1	NA
Sakamoto et al. <sup>16</sup> Japan, Yokohama City	Prospective observational	September 2008 September 2011	2 (good)	260	56.3 (90)	NR	NR	NR	69 (27) <b>at 30 d</b>	32 (12) CPC-1,2 37 (14) CPC-3,4 <b>at 30 d</b>	NR
Stub et al. <sup>31</sup> Australia, Melbourne	Prospective observational	“32 month period”	4 (fair)	9	MR	MR	MR	MR	5 (56)	3 (33)CPC-1	3/0 (type not specified)
Wang et al. <sup>18</sup> Taiwan,Taipei	Prospective observational	January 2007 September 2012	4 (good)	31	50.7 (75)	15 (48) VF/VT 16 (52) AS/PEA	NR	67.5 (no flow included)	12 (39)	8 (26) CPC-1,2	NR
<b>Totals</b>				833					<b>180 (22)</b>	<b>104 (13)<sup>g</sup> good neurologic recovery</b>	<b>34 DBD, 7 DCD and 47 not specified/15 DBD, 2 DCD</b>

LOE, Level of Evidence and study quality were assessed according ILCOR guidelines<sup>8</sup>; *No-flow* period defined as time from collapse to bystander or EMS CPR; *Low-flow* period defined as time from bystander or EMS CPR to ECPR; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; AS, asystole; DBD, organ donation after brain death; DCD, organ donation after circulatory death; MR, results were mixed with those of other study populations in publication so we are unable to present results for out of hospital cardiac arrest patients alone; NA, not applicable; NR, not reported; GOS, Glasgow Outcome Scale score; CPC, Glasgow–Pittsburgh Cerebral Performance Categories.

<sup>a</sup> Unless otherwise indicated, values presented are means for cohort studies and individual values for case studies.

<sup>b</sup> Unless otherwise indicated, values presented are medians for cohort studies and individual values for case studies.

<sup>c</sup> Study populations included a small percentage of patients whose cardiac arrest was from non-cardiac causes. The percentage of patients with non-cardiac causes were: 14% for Le Guen et al. (2011)<sup>20</sup>; 17% for Avalli et al. (2012)<sup>26</sup>; 39% for Haneya et al. (2012),<sup>24</sup> NB: in this study pulmonary embolism was considered a non-cardiac cause; and 11% for Kim et al. (2014).<sup>12</sup>

<sup>d</sup> This percentage (13%, 104/807) does not include study by Haneya et al. (2012)<sup>24</sup> as it did not report CPC score in OHCA alone.

<sup>e</sup> 44 subjects were poor function status patients. There were no organ donors since cDCD is not permitted and DBD cannot be certified under ECMO by law in Japan.

<sup>f</sup> This study has a total sample size is 27 but only 14 underwent ECPR; the rest were immediately considered as potential donors.

<sup>g</sup> Additional data not presented in publication was provided by author in the form of a personal communication.

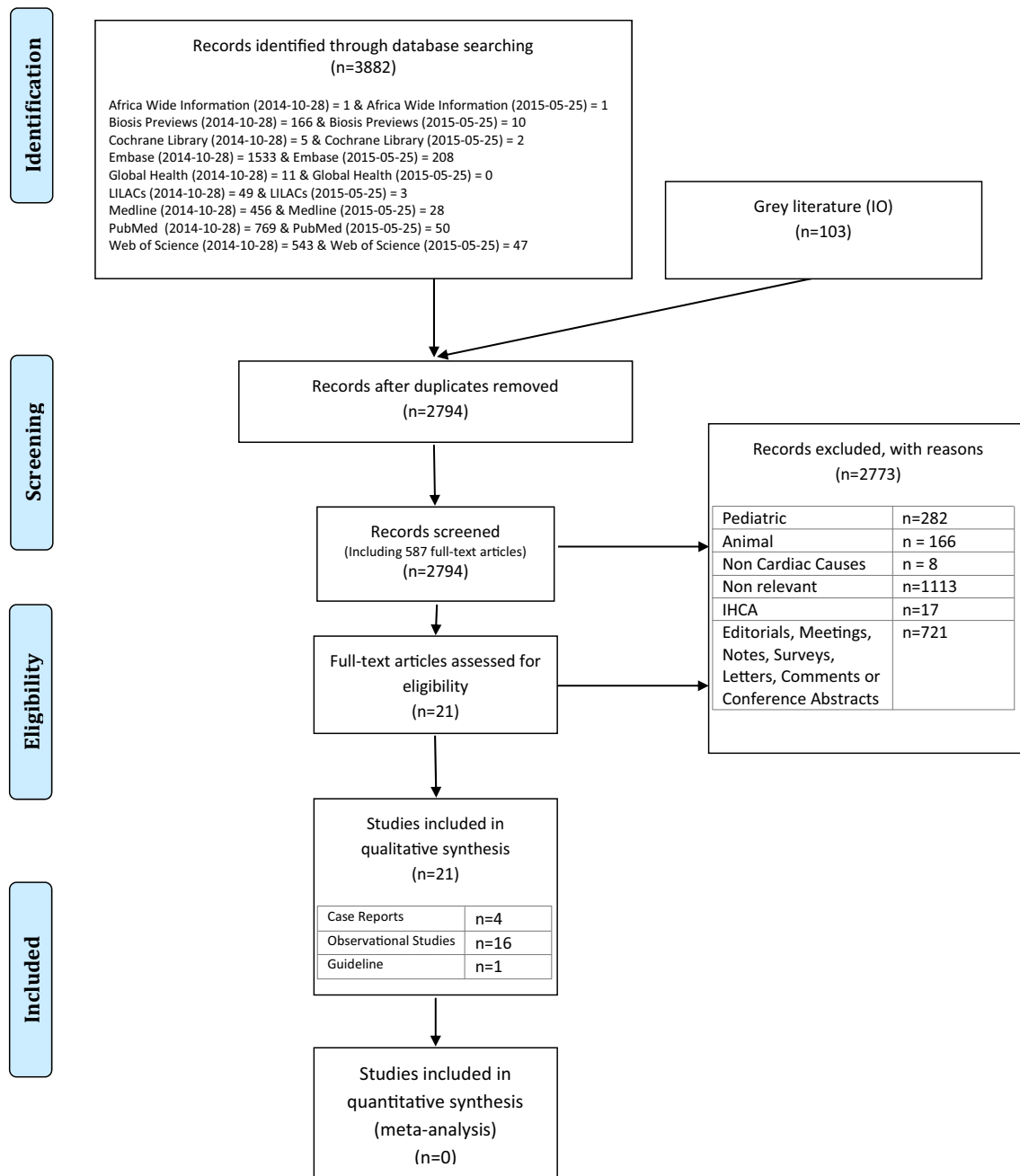


Fig. 1. PRISMA flow chart study selection.

quality (see Additional file 2) by three reviewers (IO-D, LH, FB). For the assessment of studies reporting outcomes we used the level of evidence (LOE) scale tool previously used by the International Liaison Committee on Resuscitation (ILCOR).<sup>8</sup> The guideline assessment was performed with the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument, version II.<sup>9</sup>

#### Data synthesis

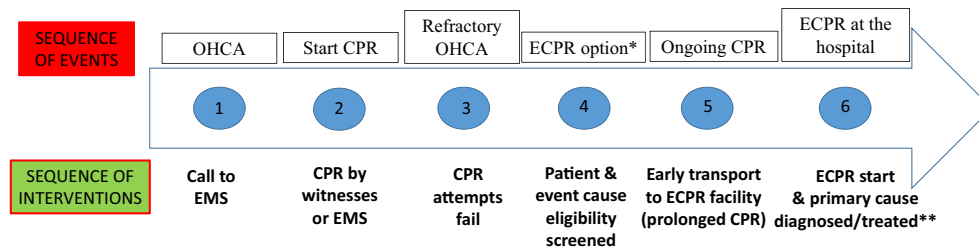
We anticipated clinical heterogeneity in selected studies due to the variability in eligibility criteria of study populations and ECPR procedures. Statistical heterogeneity was identified in relation to disparities in sample size, interventions and timelines along the OHCA process and in post-resuscitation care, as well as in the benefit/harm risk analysis. This heterogeneity also existed in the criteria for defining a good neurological recovery in survivors

and for defining potential deceased donors among non-survivors. Therefore, comparison of data was not feasible, precluding any meta-analysis. Rather, we did a tabulation of characteristics of studies (See Table 1). To reduce the heterogeneity we focused our analysis on a subgroup of patients suffering OHCA of cardiac origin. We contacted the authors of all the included studies for further details from their databases.

#### Results

A cumulative of 3882 potentially relevant citations were obtained, in addition to 103 from gray literature and 466 from citation tracking, resulting in a total of 2794 references for further review after duplicates were removed. Of these, 2773 were excluded in a first screening for the reasons specified (Fig. 1). Therefore, a final total of 21 references, 20 studies and 1 guideline, were

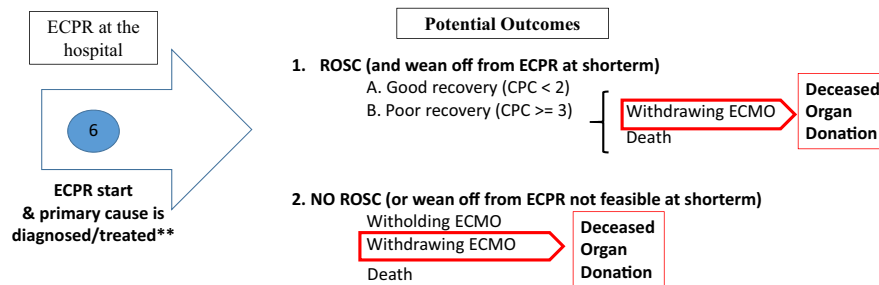
## I. Timelines and sequence of events and interventions



\* Patient must fulfill eligibility criteria & cardiac cause must be presumed/diagnosed. Then, ECPR team is early prealerted.

\*\* ECPR strategy includes a *bundle treatment* after ECPR starts (i.e.: Eco, PCI, CAGB, Thrombolysis, TTM, IABP). If ECPR fails or patient is not finally eligible for this intervention, will receive standard treatments and care according to protocols.

## II. Potential outputs of the strategy: different outcomes



\*\* ECPR strategy includes a *bundle treatment* after ECPR starts (i.e.: Eco, PCI, CAGB, Thrombolysis, TTM, IABP). If ECPR fails or patient is not finally eligible for this intervention, will receive standard treatments and care according to protocols.

Fig. 2. ECPR strategy – timelines, int and outcomes.

included in our analysis. Fig. 2 depicts timelines, events, interventions and potential outcomes during the ECPR process. Various clinical endpoints may include: ROSC with good neurological recovery (CPC 1–2); ROSC with poor neurological outcome (CPC ≥ 3) leading to poor quality survival or death and/or organ donation; no ROSC and withdrawal of ECMO leading to death and/or organ donation.

### ECPR studies

Twenty studies reporting outcomes were reviewed and are summarized in Table 1. There were no published randomized controlled trials (RCTs) although two (NCT01511666 and NCT01605409) are currently enrolling patients in Prague and Vienna.<sup>10,11</sup> Four of the selected studies were conducted in Japan, 2 in Korea and 1 in Taiwan,<sup>12–18</sup> 5 in France,<sup>19–23</sup> 2 in Germany<sup>24,25</sup> and 2 in Italy.<sup>26,27</sup> The remaining case series and reports were from Belgium,<sup>28</sup> Austria,<sup>29</sup> USA<sup>30</sup> and Australia.<sup>31</sup>

The large majority of included studies were case reports, case series, and retrospective cohort studies, all of them LOE of 4. Maekawa et al.<sup>13</sup> and Kim et al.<sup>12</sup> performed a post hoc analysis of a prospective observational study, LOE 3. Sakamoto et al.<sup>16</sup> completed a large prospective observational study (LOE 2) which is the strongest level of evidence identified. Most of the included studies presented high risk of confounding bias and threats to external validity because of their observational design. However, the methodological quality assessment of the 20 included studies resulted in a rating of *good* for 14 studies<sup>12–16,18,20,22–28</sup> and *fair* for the other 6<sup>17,19,21,29–31</sup> (see Table 1).

### Guideline appraisal

This review identified only one guideline on the specific management of refractory cardiac arrest with ECPR. It was developed

by a group of experts and endorsed by different professional societies and resuscitation boards from France. Considerations include a potentially reversible cardiac arrest cause (e.g. hypothermia or intoxication), limitations to the duration of *no-flow* and *low-flow* periods, the presence of signs of life during resuscitation as well as the level of end tidal carbon dioxide detected during the resuscitation attempts. In order to assess the rigor of clinical practice guideline development, we used the AGREE II tool. In the Additional file 2 we include the scores for each of 6 different domains. The objectives and targeted users were well described and identified. Although recommendations were presented with clarity, the domains related to the “Stakeholder Involvement”, the “Rigor of Development” and “Editorial Independence” obtained low scores. The authors acknowledged the low LOE 5 for their recommendations. Despite methodological limitations, the strength of the guideline is clarity of eligibility criteria and it provides a useful and simple decision tool for physicians and nurses in the field.

### Patient characteristics

In most studies, age of patients ranged from 16 to 75 years. The *no-flow* time periods were generally less than 5 min (range from 0 to 7) and the *low-flow* time periods were variable (range from 49 to 140, with *no-flow* period included in some studies). Factors identified as favorable prognosis included witnessed events, initial *shockable* cardiac rhythms and the identification of a potentially reversible cause of cardiac arrest. The duration of time defining failed conventional resuscitation and refractory cardiac arrest varied between studies, ranging from 10 to 30 min prior to initiating the ECPR process. The main exclusion criteria were the pre-existence of severe comorbidities, neurological disabilities, a valid *do not attempt resuscitation* order and the identification of a primary non-cardiac etiology (Table 2).

**Table 2**  
Commonly cited ECPR inclusion and exclusion criteria and bundle treatments performed.

Inclusion criteria
<ul style="list-style-type: none"> <li>• Age cutoffs, usually &lt;75 years (low end: 10 years; high end: no upper age)</li> <li>• Rhythm at the time of CPR (when included, specified as favorable to ventricular arrhythmias or “shockable” rhythms)</li> <li>• Time interval from collapse to initiation of resuscitation (no flow), generally ≤5 mins (up to &lt;15 mins)</li> <li>• Witnessed cardiac arrest</li> <li>• Etiology of arrest, to be of “presumed”, “assumed”, or “suspected” cardiac etiology</li> <li>• No ROSC despite optimal CPR, usually by 30 mins (as low as 10 mins) – refractory cardiac arrest definition</li> </ul>
Exclusion criteria
<ul style="list-style-type: none"> <li>• Do not resuscitate order</li> <li>• Severe activities-of-daily-living disability</li> <li>• Non-cardiac causes of arrest such as severe trauma, uncontrollable bleeding, irreversible brain damage, drug overdose, poisoning, submersion, etc.</li> <li>• Severe comorbidities (e.g. Often specify as those that would preclude admission to ICU, i.e. terminal illnesses, malignancies, etc.)</li> <li>• Hypothermia</li> </ul>
Bundle treatment options used during ECPR
<ul style="list-style-type: none"> <li>• Catheter Lab (e.g. PCI, CABG, etc.) ONLY: 2 studies<sup>23,30</sup></li> <li>• Catheter Lab + TTM: 8 studies<sup>12,21,22,24,25,28,29,31</sup></li> <li>• Catheter Lab + IABP: 1 study<sup>17</sup></li> <li>• Catheter Lab + IABP + TTM: 9 studies<sup>13–16,18–20,26,27</sup></li> </ul>

CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TTM, targeted temperature management, also known as therapeutic mild hypothermia; IABP, intra-aortic balloon pump.

### ECPR process

In all studies ECPR was deployed upon arrival to the hospital with a pre-alerted ECPR team on standby, except in Paris where ECPR is usually performed in the field.<sup>19,21</sup> Followed by a variable *door-to-cannulation* period of time, the *bundle treatment* approach included coronary revascularization in the catheterization lab, and in some studies adjunctive therapies were also deployed (Table 2). These co-interventions were targeted temperature management (TTM) for neurological protection and/or the use of an intra-aortic balloon pump (IABP).

### Outcomes

This systematic review identified a cumulative total of 833 patients in 20 studies. While there was some variability in time points of reported outcomes, the overall reported survival rate was 22%, including 13% having a good neurological recovery (CPC 1–2 or GOS 4–5, see Table 1). In addition to these short-term results, three studies<sup>12,13,19</sup> reported patient outcomes at 3 months with an overall survival rate of 21% (24/115), including 15% (17/115) having good neurological function and five studies<sup>16,20,22,26,30</sup> reported patient outcomes at 6 months with an overall survival rate of 16% (61/377), including 9% (34/377) having good neurological function.

Three studies<sup>19,23,26</sup> reported on potential organ donors from the group of non-survivors with anoxic brain injury, including donation after brain death (DBD) and controlled donation after circulatory determination of death (cDCD). After contacting all authors, data on organ donation outcomes were provided from 5 additional studies<sup>13,14,27,28,31</sup> (Table 1). A total of 88 potential deceased donors among non-survivors from 8 out of the 20 included studies were identified. Of these potential donors, 17 (19%) became actual donors: 15 DBD and 2 cDCD. Most donors were identified after inability of ECPR to achieve neurological recovery. However one study managed 13/27 patients as potential donors in the prehospital phase of care based on the duration of *no-flow* period of the cardiac arrest event.<sup>23</sup>

### Discussion

To our knowledge, this is the first systematic review that summarizes the defining elements and outcomes of ECPR studies in refractory OHCA of cardiac origin in adult patients. Potential outcomes of this strategy include survival with good neurological recovery, survival with poor neurological recovery, or anoxic brain injury resulting in death with or without organ donation. In order to inform practice, we have created an illustrated timeline of the ECPR process and depicted the potential scenarios and outcomes (Fig. 2).

Cumulatively, we report 833 OHCA patients in 20 studies, with an overall survival rate of 22%, including 13% with good neurological recovery. For those studies reporting longer-term outcomes, overall survival rates were 21%, including 15% good neurological function at 3 months and 16% including 9% good neurological function at 6 months. Eight of twenty studies outlined 88 potential organ donors, 19% of which became actual organ donors. The vast majority of previously reported outcomes are related to in-hospital cardiac arrest and do not report neurological or organ donation outcomes. Although this review focuses on refractory OHCA of cardiac origin, the results are comparable to previous adult ECPR reports that include various mixes of in/out of hospital cardiac arrest and cardiogenic shock.<sup>32</sup> Previously reported survival rates to hospital discharge range from 29 to 47%, including the large Extracorporeal Life Support Organization (ELSO) registry report of 4200 ECPR patients.<sup>6,33,34</sup>

Given that this review is based largely on existing case reports, case series or small observational studies, heterogeneity was evidenced in both populations and interventions. There is variability in patient selection, age limits, duration of *no-flow*, the moment when the OHCA is considered refractory to conventional resuscitation, logistics and clinical pathways, time from cardiac arrest to cannulation, interventions deployed, and levels of care provided before and after ROSC. The decision to offer ECPR was often made on a case-by-case basis at the discretion of the resuscitation team leader,<sup>12,14,18,35</sup> which may lead to reporting bias.<sup>36</sup> Randomized controlled trials in OHCA are registered (NCT01511666 and NCT01605409), and currently enrolling patients.<sup>10,11</sup>

What remains unresolved are the optimal patient characteristics, variables associated with good neurological outcomes and the cost-benefit analysis of this complex and resource intensive intervention.<sup>3,37</sup> The main variables determining neurological outcome<sup>38,39</sup> presumably are: the duration without cardiac output until resuscitation begins (*no-flow* period), quality of CPR, and the duration with low cardiac output during resuscitation attempts (*low-flow* period). ILCOR reviews<sup>40,41</sup> suggest that the presence of witnesses, shorter duration of resuscitation prior to ECPR, a *shockable* initial rhythm, and the early identification/treatment of the reversible cause of arrest were factors positively associated with survival to discharge. Although the ILCOR does not recommend the ECPR strategy routinely, it states that in settings where it can be rapidly implemented, ECPR may be considered for select cardiac arrest patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support (Class IIb, LOE C-LD).<sup>42</sup>

Innovative strategies seeking to minimize the *no-to-low flow* period include cannulation in the field followed by rapid deployment of mobile ECPR.<sup>19,21</sup> The effectiveness should be compared to early transport under high-quality ongoing resuscitation and ECPR institution after arrival to the hospital. Novel therapies are in evolution<sup>43,44</sup> to enhance cardiac and neurological recovery (Table 2), including percutaneous coronary intervention, intra-aortic balloon pump, thrombolysis and targeted temperature management. When offered during or early after resuscitation attempts, results were encouraging.<sup>13,16,31,45–47</sup>

In addition to survival outcomes, this review suggests that organ donation after death, while poorly reported, should be included as a relevant outcome in ECPR studies. It is likely that the number of potential donors with irreversible anoxic brain injury may be underestimated as some jurisdictions do not offer donation option under these circumstances. For example, through personal correspondence, Maekawa<sup>13</sup> reported 44 patients with a poor neurological outcome following ECPR, but explained that at the time of the study, controlled DCD was not performed in Japan, and DBD could only be certified in hemodynamically stable patients which exclude ECPR.

Any innovative resuscitation intervention that improves patient outcome has direct benefits to the patient, and may have an indirect societal benefit arising from patients who will inevitably die but can become organ donors. However, these positive consequences must also be balanced by the potential for undesirable outcomes. Some authors have reported higher survival with good neurological recovery compared to conventional resuscitation, but also higher rates of coma and permanent vegetative state.<sup>12,16</sup> Thus, it has been stated that the ECPR strategy can lead to the so-called *bridge to nowhere* in which a patient, not likely to recover, not going to die, is dependent on ongoing life support,<sup>36</sup> posing burdens to patient, family and the health care system. However, this review demonstrates that survival with poor neurological outcome overall was 9% and for those studies reporting outcomes at 3 and 6 months it was 6% and 7%, respectively.

This systematic review has several limitations. Study heterogeneity precluded a meta-analysis preventing any meaningful comparison between protocols, interventions and outcomes. The lack of standardization of definitions at each step of the process and the lack of homogeneity of good outcomes and follow-up times for survivors hindered a more consistent and clear presentation of results. Finally, we were unable to perform any guideline comparisons; only one guideline was identified. Despite these limitations, ECPR is feasible for refractory OHCA of cardiac origin in adult patients. ECPR may increase the neurologically good survival in selected patients. Prospective studies are required to clarify patient selection and modifiable outcome variables. Further investigation is needed to determine whether ECPR cannulation is more effective when performed in pre-hospital or in-hospital settings. A cost-effectiveness analysis of the ECPR strategy is required to inform policy. The deceased organ donation option may be considered a secondary outcome when patient survival with quality of life is not achieved.

## Conclusions

This systematic review describes and compares the international variability in practices, protocols and outcomes for the ECPR strategy in adult patients who suffered a refractory OHCA, informing future protocol development and health policy. The review highlights the need for standardization of definitions and of study outcomes to improve study homogeneity and clarity of findings. We advocate, aligned with ILCOR recommendations,<sup>48</sup> that future studies report the following outcomes: survival and neurological status (CPC score) at 24 h, 1 month, 3 months, 6 months and 1 year as well as outcomes pertaining to organ donation potential in non-survivors such as the mechanism (neurologic versus circulatory) of death and the number of actual donors.

The ECPR strategy is a viable last option for increasing the probability of survival in a potentially hopeless scenario. A bundle of novel therapies are feasible to treat preselected adult patients suffering from a refractory OHCA of cardiac origin. The process includes ECPR and other co-interventions such as percutaneous coronary intervention, intra-aortic balloon pump, thrombolysis

and targeted temperature management. When deployed during and/or soon after resuscitation attempts, despite variations in practice and heterogeneity of outcomes, these interventions yield a good neurological survival in 12% of adults suffering a refractory OHCA. Importantly, prior to ECPR strategy implementation, these patients would not have had practically any chance for survival. Moreover, this strategy has the potential to increase the pool of solid organs available for transplant from non-survivors. This secondary outcome should not be disregarded, from a cost-effectiveness point of view, in a global context of organ shortage; it may be a more comprehensive approach to the end-of-life scenario drawn by sudden cardiac arrest events, a major public health burden worldwide.

## Author's contributions

IO-D and LH carried out the systematic review, conceived of the protocol and drafted the manuscript. SDS and FB supervised and participated in the review of study selection and in the quality assessment process. EG carried out the search strategy and led the management of references, designing the figures related to this part. All authors critically reviewed and approved the final manuscript.

## Conflict of interest statement

LH is a paid research consultant for Canadian Blood Services. The other authors declare that they have no competing interests.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.resuscitation.2016.01.018>.

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