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REVIEW ARTICLE

Cardiology

Extracorporeal cardiopulmonary resuscitation for refractory out-of-hospital cardiac arrest: Lessons learned from recent clinical trials

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Abstract

Cardiac arrest is a leading contributor to morbidity and mortality in the United States. Survival has been historically dependent on high-quality cardiopulmonary resuscitation (CPR) and rapid defibrillation. However, a large percentage of patients remain in refractory cardiac arrest despite adherence to structured advanced cardiac life support algorithms in which these factors are emphasized. Veno-arterial extracorporeal membrane oxygenation is becoming an increasingly used rescue therapy for patients in refractory cardiac arrest to restore oxygen delivery by extracorporeal CPR (ECPR). Recently published clinical trials have provided new insights into ECPR for patients who sustain an outside hospital cardiac arrest (OHCA). In this narrative review, we summarize the rationale for, results of, and remaining questions from these recently published clinical trials. The existing observational data combined with the latest clinical trials suggest ECPR improves mortality in patients in refractory arrest. However, a mixed methods trial is essential to understand the complexity, context, and effectiveness of implementing an ECPR program.

1 | INTRODUCTION

Cardiac arrest is a leading contributor to morbidity and mortality in the United States. Despite decades of clinical trials and advancements in resuscitation algorithms, survival remains poor and stubbornly unchanged, with only 25% of in-hospital cardiac arrest (IHCA) and 10% of outside-hospital cardiac arrests (OHCA) surviving to hospital discharge,[1–10] albeit with some variation among systems.[11] Early, effective cardiopulmonary resuscitation (CPR) and rapid defibrillation are among the few resuscitation strategies that consistently demonstrate improved neurologically favorable survival after cardiac arrest.

Even with early structured advanced cardiac life support (ACLS) in the pre-hospital setting, up to 75% of patients remain in

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refractory arrest.[12] Some of these patients may benefit from veno-arterial extracorporeal membrane oxygenation (VA-ECMO), which has piqued interest for years as a potential means of restoring vital organ oxygen delivery by extracorporeal CPR (ECPR). The 2015 Institute of Medicine report on cardiac arrest recognized ECPR as an emerging technology for some patients and urged further development and research.[13] The American Heart Association's position, as recent as 2020, has remained consistent that the evidence does not support a recommendation for ECPR; however, it may be considered in select patients who have a potentially reversible disease with a limited period of extracorporeal support.[14–16] The European Resuscitation Council guidelines in 2021 suggest considering ECPR for selected refractory cardiac arrest patients in settings in which it can be implemented.[17] Recently published clinical trials have provided new insights into ECPR for OHCA.

In this paper, we summarize the rationale for, results of, and remaining questions from these first ever clinical trials. Articles published in major databases (PubMed/MEDLINE) were identified by search for "ECPR," "Refractory Cardiac Arrest," and "ECLS." In-text citations were used as indicated. The aim of this narrative review is to compare and contrast important insights, similarities, and differences among the three most recent randomized controlled trials. Data from pertinent observational studies, systematic reviews, metanalysis, and subsequent secondary analyses are included where appropriate to provide context.

2 | RATIONALE FOR ECPR

VA-ECMO provides both hemodynamic and respiratory support for patients in cardiopulmonary failure, usually from a reversible cause of cardiogenic shock or as a bridge to heart transplant or durable device. When VA-ECMO is used for patients in refractory cardiac arrest as ECPR, the hemodynamics and gas exchange are entirely supported by ECMO.

ECPR is initiated by percutaneously placing femoral venous and arterial cannulae under ultrasound guidance. A large (19-25 Fr) venous drainage cannula is inserted into a femoral vein, usually the right side, up to the inferior vena cava near the junction with the hepatic vein and a 15–17 Fr arterial cannula is placed in the right or left femoral arteries. The cannulas are then connected to a pre-primed ECMO circuit, where flow rates are determined by the cannulae size (venous more so than arterial) and pump speed, but often exceeds 4 L/min. The patient is anticoagulated, can be rapidly target temperature controlled, and chest compressions can be discontinued and vasopressors weaned at this point.

In the presence of no or very low native cardiac output, hemodynamics and gas exchange are completely supported by ECMO as the retrograde flow of oxygenated blood up the descending aorta to the aortic arch and coronary arteries and downstream to essential organs. However, there are two major concerns. First, the leg with the arterial cannula gets little to no blood flow, depending on the amount of arterial occlusion from the size of the arterial cannula and vasospasm from epinephrine given during the arrest. A 5Fr distal perfusion cannula can be inserted and connected to the circuit to perfuse the leg. Second, if the left ventricle is unable to eject a stroke volume against the afterload imposed by the retrograde aortic flow, it tends to dilate and ultimately becomes ischemic or an intracardiac thrombus can form. In this case, the LV needs decompressed by one of a multitude of options.[18] Essentially, VA-ECMO as ECPR only buys time to diagnose and treat the underlying cause of the cardiac arrest.[19–21]

TABLE 1 Factors associated with improved extracorporeal CPR (ECPR) survival.

Age < 65 years
No comorbidities
Witnessed arrest with bystander CPR
Shockable rhythm
CPR onset to cannulation < 60 min

Abbreviation: CPR, cardiopulmonary resuscitation.

Data on patients with in-hospital cardiac arrest show that, despite more common comorbidities and non-shockable rhythms, outcomes are better with ECPR.[7,22,23] The data are largely observational, with selection bias and confounders, but consistently show an association between *early* ECPR and improved outcomes,[19,24–30] and improved outcomes compared to ECPR for OHCA.[23,31] Observational studies on OHCA have mixed findings, but with optimal patient selection (Table 1) and early cannulation, ECPR shows an association with improved outcomes.[23,32–41]

Two prospective observational studies evaluated early, invasive bundles of care that included ECPR for patients with refractory cardiac arrest from ventricular tachycardia or fibrillation. These studies found that such a bundle is both feasible[42] and associated with improved outcomes compared to conventional care after cardiac arrest.[43] Taken together, the literature on ECPR for OHCA suggests some survival advantage with optimal patient selection and early cannulation. Unfortunately, the number of cardiac arrest patients in the United States that meet such inclusion criteria is few (<10% of all arrests).[44,45]

While there are clear potential benefits for some patients with ECPR, there is another side to that coin. Complication rates of ECPR are not trivial.[46–48] Bleeding is the most common complication, reported at vascular insertion sites, brain, gastrointestinal tract, as well as adverse events including pulmonary hemorrhage and pericardial effusions (altogether reported in about one-third of patients, but as high as 70%).[49] Additionally, substantial multi-institutional investment and coordination is required to provide 24/7 ECPR support for a community. The time from arrest to cannulation exceeds 60 min in half of patients,[50] which is the threshold where the survival rate with ECPR starts to dramatically fall,[51,52] which only happened around half the time in a recent feasibility study. There are significant resources required to meet such highly demanding timelines. EMS systems may need to change operating procedures and the flow of patients may need to change within a community, bypassing the nearest hospital for the nearest ECPR-capable center. Within a given hospital, equipment,

TABLE 2 Outcome of interest in the three recent veno-arterial extracorporeal membrane oxygenation (VA-ECMO) clinical trials.

Outcome	ARREST	PRAGUE	INCEPTION
30-day survival with CPC 1-2		31% vs. 18% ($p = 0.02$)	**20% vs. 16% [OR 1.4 (0.5–3.5)]**
180-day survival with CPC 1-2		**31.5% vs. 22% (ns)**	20% vs. 16% [OR 1.3 (0.05–3.5)]
Survival to hospital discharge	**43% vs. 7%**		

Note: The primary outcome for each trial is in bold text.
Abbreviations: CPC, cerebral performance category; OR, odds ratio; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

personnel, and space need to be dedicated at all times to meet these goals should an ECPR eligible patient arrive. Thus, there has been a need for high-quality prospective trials to determine the effectiveness of ECPR that would warrant such an investment.

3 | RECENT CLINICAL TRIALS ON ECPR

In the last 3 years, three such trials have been published, along with an increasing number of meta-analyses and secondary analyses. The studies provide promising, yet conflicting results for ECPR (Table 2).

3.1 | ARREST trial

The ARREST trial was the first randomized clinical trial in the United States designed to assess the safety and feasibility of an ECPR-facilitated resuscitation versus standard ACLS for refractory OHCA.[53] This was a phase 2 single center, open-label randomized trial that included consecutive adults (18–75 years old) with an initial shockable rhythm, no return of spontaneous circulation (ROSC) after three shocks, body morphology amenable to mechanical compression device, and an estimated transfer time to the emergency department <30 min. The trial tested two intervention arms, an ECPR-facilitated resuscitation strategy and a standard ACLS strategy. In the ECPR-facilitated resuscitation arm, participants went straight to the cardiac catheterization laboratory. At that point, in patients undergoing CPR, an arterial blood gas was obtained to evaluate termination criteria (≥2 of end-tidal CO2 < 10 mm Hg, PaO2 < 50 mm Hg or oxygen saturation < 85%, and lactic acid > 18 mmol/L). If termination criteria were not met, VA-ECMO was initiated, and an angiogram performed in all patients, with revascularization if a culprit lesion was identified. For participants with ROSC, an angiogram was performed with concurrent revascularization if indicated and hemodynamic support as needed. In the ACLS strategy arm, participants remained in the ED for at least 15 min after arrival or for at least 60 min after the 911 call. If ROSC was obtained at any point, the participant underwent angiography, revascularization, and circulatory support as needed.

The primary outcome was defined as survival to hospital discharge. Secondary endpoints included survival with a modified Rankin score ≤3 and a cerebral performance category scale of ≤2 at 3 and 6 months. The trial was stopped early by the data safety monitoring board (DSMB) due to meeting stopping criteria for superiority (≥98.6% posterior probability of difference in the primary outcome) in the ECMO-facilitated arm after 30 subjects were enrolled (of the planned 150 subjects). The survival to hospital discharge in the ECPR group was 43% versus 7% for the conventional CPR group (posterior probability 98.6%).

3.2 | Prague OHCA trial

The second trial, Prague OHCA Trial, was also a single-center randomized controlled trial. Eligible patients included OHCA patients with a presumed cardiac etiology, an initial shockable rhythm, and at least 5 min of conventional CPR without ROSC.[54] For eligible patients, a pre-alert paging system was used by the prehospital system to alert the clinical teams and the research staff, who randomized the participant into one of two arms: an invasive strategy or standard ACLS strategy. If randomized to the standard strategy arm, standard resuscitation was pursued in the field. However, if randomized to the invasive strategy, intra-arrest cooling was initiated, and participants were transported directly to the cardiac catheterization laboratory for VA-ECMO cannulation and angiography with the intention of revascularization.

The primary outcome was defined as 180-day survival with a cerebral performance category scale of ≤2. Secondary outcomes included 30-day survival with cardiac recovery and neurologic recovery (CPC 1 or 2) within the 30 days after the OHCA. This trial was also stopped early for crossing the statistical bounds for futility at the interim analysis after 256 participants were randomized. The ECPR group had a 31.5% 180-day survival with good neurologic outcome, while the conventional group had a 22% survival. Importantly, crossover from the standard arm to the invasive strategy arm was allowed in this trial specifically after two additional unsuccessful defibrillations were reported at the request of the emergency physician. Crossover in the other direction, from the invasive strategy to the standard arm, was allowed if further resuscitation was deemed to be futile. There were a total of 20 crossovers or 7.6% of the total enrollment population. Generous crossover between groups may have contributed a selection bias that ultimately led to statistical confounding and a higher than expected survival in the standard strategy arm.

Subgroup analysis suggested that if the arrest was due to coronary artery disease and there was a shockable rhythm, there was a benefit from an early invasive strategy. Secondary analyses using Cox proportional hazard models to correct for confounders showed a clear benefit to having an early invasive strategy.[55] A Bayesian re-analysis showed convincing posterior probabilities favoring an early invasive strategy regardless of the prior probabilities used,[56] and a secondary

analysis pooling ARREST and Prague data showed a significant benefit in all outcomes with ECPR.[57] One systematic review and meta-analysis of propensity-matched observational studies with inclusion of these clinical trials illustrated a 6.2% absolute survival with good neurologic outcome improvement with ECPR (14% vs. 7.8%, odds ratio [OR] 2.11, 1.41–3.15).[58]

3.3 | INCEPTION trial

The most recent trial, INCEPTION, was the first multicenter randomized trial of OHCA patients across 10 institutions in the Netherlands.[59] Patients 18–70 years old were eligible if they had refractory OHCA, defined as no ROSC after at least 15 min of ACLS with an initial shockable ventricular rhythm. After three cycles of CPR, EMS agencies then placed a mechanical compression device and a supraglottic airway for rapid transport to the receiving hospital. Patient information was relayed to the receiving hospital during transport and the research team randomized the patient prior to arrival to either receive ECPR or to continue standard care. While *expected* time between cardiac arrest and cannulation (i.e., low-flow time) >60 min was an exclusion criterion, participants still received the intervention if the *actual* time was longer than 60 min, honoring intention to treat principles since randomization occurred prior to arrival. Consistent with the other trials, post-resuscitation care was per guidelines and local protocols. Post-ROSC care was 33 degrees for 24 h and then afebrile for 72 h, and included all of the bundle of usual post-ROSC care as dictated by the European resuscitation guidelines, but it was not protocolized. Another important distinction in this study was that neuroprognostication occurred at 72 h.

The primary outcome was defined as 30-day survival with a cerebral performance category scale of ≤2. Secondary outcomes included 30-day survival with cardiac recovery and neurologic recovery (CPC 1 or 2) within the 30 days after OHCA. This trial enrolled 134 participants in the intention-to-treat analysis. Of the 70 participants randomized to receive ECPR, 18 (26%) were not cannulated mostly due to ROSC prior to cannulation. Similarly, 12 (19%) of the participants randomized to receive standard care either achieved ROSC (9) or underwent ECPR (3). While the trial went to full enrollment, there was statistically no difference in 30-day survival with favorable neurologic outcome between the ECPR (20%) and conventional care (16%) groups (OR, 1.4; 95% confidence interval, 0.5–3.5; $p = 0.52$). A Bayesian secondary analysis showed only modest posterior probabilities for a meaningful effect on survival,[60] and a per-protocol analysis showed a nonstatistically significant improved survival with ECPR.[61]

4 | KEY CONSIDERATIONS

ECPR functions as a bridge-to-treatment by augmenting CPR with temporary hemodynamic support. The advantage of rapidly shortening low-flow time with ECPR is potentially unparalleled in cardiac arrest care.[62] The goal time from arrest to cannulation is <60 min, but average times in these three trials were 59 min (ARREST), 61 min (Prague), and 74 min (INCEPTION). Additionally, ECPR allows ongoing organ support to prolong time available to investigate the underlying etiology and revascularize, yet cannulation was unsuccessful in about 10% of patients in the only trial to report this.[54] Overall, ECPR has the potential to dramatically improve cardiac arrest survival, yet there are disparate results in these three clinical trials and the interpretations of their data.

There are several considerations when reviewing these trials together. One single-center trial (ARREST), designed for safety and efficacy as it was a phase 2 trial, was stopped early for clear efficacy, while another single-center trial (Prague) was stopped early for crossing the stopping bounds for futility. The only multi-center trial (INCEPTION) went to full enrollment but failed to show benefit. How are these differences reconciled? One important point is the complexity in determining study futility. The Prague trial was stopped for crossing the statistical bounds for futility, which means continuing the trial was futile as it was statistically impossible that full enrollment will be able to show a significant difference in the pre-planned survival benefit. It means that continuing the trial is futile, not necessarily that the intervention itself is futile.

The patient populations and the intervention itself differed between trials, thus the comparisons themselves were different (Table 3). ARREST compared ECMO-facilitated resuscitation to standard care with the most liberal upper age limit at 75 years. The Prague trial and INCEPTION, on the other hand, compared early invasive strategies to standard of care with more restrictive upper age limits (Prague: 65 years, INCEPTION: 70 years) and only two-thirds of subjects received ECPR, particularly because of how each trial handled ROSC. The Prague trial also implemented prehospital hypothermia. ARREST did not directly require a witnessed arrest (only that initial rhythm was shockable), whereas both Prague and INCEPTION required witnessed arrest for inclusion. However, 24/30 ARREST patients were witnessed and the prehospital time intervals are consistent with the other trials. The trials also differed in their specific language about excluding chronic disease, but with similar intent resulting in similar comorbidity demographics between trials. The INCEPTION trial randomized participants while in transport and still included participants if their actual interval from arrest to arrival was greater than 60 min, while an estimated transport time >30 min was an exclusion for ARREST patients, who were randomized on arrival to the hospital.

Cannulation was different between the trials as well, and when combined with the longer duration from arrest to cannulation, it has become a particular critique of INCEPTION. Cannulation in the INCEPTION trial was performed per protocol for the individual hospital. Conversely, in ARREST and in the Prague trial, ECPR participants went straight to the cardiac catheterization lab and were cannulated there by a single group of investigators. This critique of INCEPTION is often raised but there is no strong objective data that it is indeed a weakness of the trial. According to the INCEPTION supplementary material, there are only 16 cardiac surgery centers in the Netherlands that do a combined 15,000 annual cardiac cases. Of these, 10 centers that all have experience in ECMO cannulation in unstable patients

TABLE 3 Key data elements on the three recent veno-arterial extracorporeal membrane oxygenation (VA-ECMO) clinical trials.

	ARREST	PRAGUE	INCEPTION
Inclusion criteria	18–75 years OHCA Unwitnessed or witnessed arrest Initial shockable rhythm No ROSC within 3 defibrillations[a] Transfer time < 30 min	18–65 years OHCA Witnessed arrest Presumed cardiac etiology Minimum of 5 min of CPR without ROSC	18–70 years OHCA Witnessed arrest Initial shockable rhythm 15 min of CPR Expected arrest-ED $\leq$ 60 min
Key exclusion criteria	Two or more: $ETCO_2$ < 10 mmHg PaO_2 < 50 mmHg or SpO_2 < 85% Lactic acid > 18 mmol/L Severe concomitant illness	Unwitnessed arrest ROSC within 5 min Known severe organ dysfunction	ROSC Actual interval > 60 min Terminal heart failure or severe COPD
Enrollment strategy	Randomization after arrival	Pre-alert and randomization	Pre-alert and randomization
Consent strategy	EFIC	Delayed written LAR consent	Deferred consent
Cannulation protocol	Cath lab	Cath lab	Per local protocols (cardiac surgery)
Time intervals:			
Arrest to EMS arrival	6–7 min	8 min	8 min
Arrest to randomization	48.5–51.8 min	24–26 min	32[b] (10) min
Arrest to ED arrival		49–60 min	36[b] (12) min
Arrest to ECLS flow	59[b] (28) min	61–62 min	74[b] (15) min
Post-resuscitation care	Local guidelines 24 h TTM to 34 degrees No neuroprognostication for at least 72 h after arrest	Standardized based on European Resuscitation Council Guidelines	Per local and European Resuscitation Council Guidelines
Primary outcome	Survival to hospital discharge	Survival with a favorable neurological outcome at 180 days (CPC 1-2)	Survival with a favorable neurological outcome at 30 days (CPC 1-2)

Abbreviations: COPD, chronic obstructive pulmonary disease; CPC, cerebral performance category.; CPR, cardiopulmonary resuscitation; EFIC, exception from informed consent; LAR, legal authorized representative; OHCA, outside hospital cardiac arrest; ROSC, return of spontaneous circulation; TTM, target temperature management.

[a]ROSC after third shock is eligible for inclusion.

[b]Data presented as mean (standard deviation) as reported in the publications.

participated in the trial. Of these 10, the overwhelming majority of participants (84%) came from five centers and were cannulated by one of six people (three cardiac surgeons, two interventional cardiologists, and one intensivist); see table S2 in their appendix. From these data, there is no indication in these data to support inexperience as a confounder.

While not specifically part of the intervention for each trial, post resuscitation care is also a variable that requires consideration as it will affect outcomes. Post-ROSC care in the INCEPTION trial was per European Resuscitation Council guidelines. The Prague trial had standardized post-ROSC care based on the European Resuscitation Council guidelines, and the ARREST trial was per local guidelines. The multicenter nature of the INCEPTION trial likely adds some confounding to the post arrest care compared to the single center studies. The effect of post-ROSC care variability on patient survival, morbidity, neuroprognostication, and withdrawal of life support is an unquantified confounding variable across centers and is a key logistical and implementation consideration for programs and trials going forward.

Another key consideration is the outcome of interest, which differed between each trial from hospital survival (ARREST) to either 30-day (INCEPTION) or 180-day (PRAGUE) neurologically favorable survival (Table 2). INCEPTION failed to show a difference (20% vs. 16%), but the baseline survival with conventional CPR was higher than the global average and twice as high as what they had powered for. The Prague trial was very similar, with around a 20% neurologically intact survival rate for conventional CPR. The ARREST trial looked at patient survival to hospital discharge, which was quite imbalanced toward early invasive strategy with ECPR.

There have been many systematic reviews and meta-analyses published further evaluating these trials with varying results. Two found no difference in outcomes at 6 months,[63] or at the shortest reported time interval.[64] Two others found ECPR was superior at the longest reported time interval.[65,66] One systematic review with both

a meta-analysis and trial sequential analysis that included these three trials showed a benefit with ECPR for patients with in-hospital cardiac arrest but failed to show a benefit for OHCA. Yet, the trial sequential analysis suggested more patients were needed.[67]

5 | UNRESOLVED QUESTIONS

5.1 | What is the potential impact of ECPR?

The ARREST Trial took 11 months to enroll 30 participants. In the Prague trial, 4345 patients were assessed for eligibility over 91 months to enroll 264 participants out of 358 patients with refractory arrest. The INCEPTION trial lasted 45 months with a brief pause during the pandemic to enroll 134 participants. Thus, trial enrollment in both the Prague and INCEPTION trials was roughly 3%–5% of patients with OHCA. In all three trials, this adds up to about three patients with OHCA per month potentially eligible for ECPR. A recent publication on the experience in Los Angeles showed similar outcomes and time intervals at their cardiac arrest receiving hospitals as the recent published trials, with survival to discharge of 27% for ECPR versus 14% for conventional care.[68] In this study, there were about one and a half cases per month. Similarly, a large observational geographic study evaluated the potential impact of ECPR by evaluating changes to inclusion criteria and transport times to ECPR-ready or capable centers in the United States. They found that regardless of the changes to inclusion criteria or desired transport times, the ECPR potential cases remain around 3% of all OHCA cases.[69]

While ECPR may benefit some patients with refractory OHCA, there are other potential impacts of ECPR. Nonneurologically intact survivors with cardiac recovery will require prolonged and likely expensive long-term care, and neurologically intact survivors without cardiac recovery will impose an ethical dilemma on families and caregivers if they are not candidates for durable devices or transplant. On the other hand, patients that meet brain-death criteria may be an important patient population to increase organ donation options.[70] For those that do survive neurologically intact, the cost-effectiveness for quality-adjusted life years appears to be acceptable, and similar to that for organ transplantation,[71] although more data are needed.

5.2 | What is the feasibility and effect of implementing an ECPR system?

When evaluating the body of evidence as a whole, doing another effectiveness trial would be large, expensive, prolonged, and unlikely to add significant knowledge given that, on the balance of evidence, ECPR is likely to benefit *a patient* with refractory OHCA compared to standard cardiopulmonary resuscitation. Thus, the major knowledge gap is not if ECPR benefits a single patient with OHCA, but rather what the effect of implementing an ECPR system is. How feasible is it to broadly implement an ECPR system? What disparities in care delivery and outcomes are uncovered across care service areas? ECPR requires an efficient, resource-intensive, multidisciplinary team, and multi-institutional coordination. Such integration confers challenges when extrapolating this intervention beyond academic tertiary care centers, and even among them.

Successful ECPR requires the right patient under the right clinical scenario to present to the right healthcare system in the right amount of time and at the right time with the right people available and prepared. Connecting these variables is a major challenge, requiring the implementation of ECLS into community practice and with public investment. This will require strategies to quickly identify and transport appropriate patients to capable facilities in a timely manner, most likely requiring modifications to EMS protocols and receiving hospital capabilities. Individual treatment facilities will also require cost investments to scale resources, build multidisciplinary teams, educate staff for ECPR, and scale resources for potentially increased length of hospital stay in the cardiac patient. Designing a program with sufficient cannulation experience to provide 24/7 availability while maintaining quality despite an overall low volume will be a significant programmatic challenge, especially if ECPR is offered at many hospitals in a particular region.

It may also raise difficult ethical considerations as to how ECLS can become more uniformly available without furthering already existing inequities in care access. Lastly, what will the effect be on the outcomes of patients with OHCA that do not receive ECPR as the systems are geared to the minority of patients that do receive ECPR? Will neurologically intact survival in patients that do not receive ECPR improve, or worsen, given that early intra-arrest transport for ECPR is critical for a survival advantage with ECPR[37] but detrimental for patients that do not get ECPR?[72] What will it take to implement quality ECPR to affect the most possible people without worsening the outcomes for patients not eligible for ECPR?

6 | CONCLUSION

The existing observational data combined with these new trials suggest ECPR improves mortality for patients with refractory OHCA. The feasibility and effect of implementation of an ECPR-capable system on the public health burden of OHCA requires further study and remains an important knowledge gap. A mixed methods trial is required to fill these knowledge gaps and to advance our understanding of the feasibility, impact, and cost of ECPR.

AUTHOR CONTRIBUTIONS

Jarrod Mosier and Lisa Merck conceptualized the paper. Stephanie DeMasi and Megan Donohue wrote the initial draft. All authors critically reviewed, edited, and approved for publication. The manuscript was reviewed and approved by the SIREN executive committee.

CONFLICT OF INTEREST STATEMENT

Stephanie DeMasi and Megan Donohue report no disclosures, Lisa Merck and Jarrod Mosier are primary investigators for the SIREN CORE-EM Hub alliance under NINDS/NHLBI 2 U24NS100673-06.

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