ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Extracorporeal Membrane Oxygenation for Cardiac Indications in Adults: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

Cardiac arrest and cardiogenic shock are medical emergencies in which the heart suddenly stops beating properly and/or cannot pump enough oxygen-rich blood to other vital organs. For cardiac arrest, usual emergency care is cardiopulmonary resuscitation (CPR)—manual chest compression and artificial breathing to keep the person alive until their heart restarts or they can have other life-saving treatment. For cardiogenic shock, usual emergency care includes drugs and/or small mechanical pumps implanted under the skin or via more invasive surgery.

Extracorporeal membrane oxygenation (ECMO) is another type of rescue therapy that can be used for cardiac arrest and cardiogenic shock. It is a life support machine that does the work of the heart and lungs, allowing them to rest until time or additional procedures reverse the problem that caused them to fail. When used for cardiac arrest, ECMO is also called extracorporeal (outside the body) CPR, or ECPR.

This health technology assessment looked at how safe, effective, and cost-effective ECMO is for treating adults with cardiac arrest or cardiogenic shock when they do not respond to usual emergency care. It also looked at the budget impact of publicly funding ECMO and at the experiences, preferences, and values of people who have had experience with ECMO due to cardiogenic shock.

What Did This Health Technology Assessment Find?

Using ECMO to treat adults with cardiac arrest may reduce brain damage and deaths, compared with using only conventional CPR. For treating cardiogenic shock, ECMO may reduce deaths compared with some, but not all, types of conventional procedures. Problems with the quality of the available studies mean we are not very confident in their findings.

Our cost-effectiveness analysis indicated that compared with conventional CPR, ECMO may be cost-effective for treating adults with cardiac arrest. There was not enough evidence available for us to evaluate the cost-effectiveness of ECMO for treating cardiogenic shock. We estimate that publicly funding ECMO for people with cardiac arrest and cardiogenic shock in Ontario over the next 5 years would cost about $845,000 to $2.2 million per year.

The patients and family members we spoke with had limited ability to assess the impact of ECMO, due to the serious medical situations in which they experienced the procedure. Overall, participants were grateful this life-saving device was available and able to stabilize their or their loved one's acute condition.

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ABSTRACT

Background

Extracorporeal membrane oxygenation (ECMO) is a rescue therapy used to stabilize patients with hemodynamic compromise such as refractory cardiogenic shock or cardiac arrest. When used for cardiac arrest, ECMO is also known as extracorporeal cardiopulmonary resuscitation (ECPR). We conducted a health technology assessment of venoarterial ECMO for adults (aged ≥ 18 years) with cardiac arrest refractory to conventional cardiopulmonary resuscitation (CPR) or with cardiogenic shock refractory to conventional medical management (i.e., drugs, mechanical support such as intra-aortic balloon pump and temporary ventricular assist devices). Our assessment included an evaluation of effectiveness, safety, cost-effectiveness, the budget impact of publicly funding ECMO for these indications, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Risk of Bias in Systematic Reviews (ROBIS) tool for systematic reviews and the Risk of Bias Among Nonrandomized Trials (ROBINS-I) tool for observational studies, and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted a cost-effectiveness analysis with a lifetime horizon from a public payer perspective. We also analyzed the budget impact of publicly funding ECMO in Ontario for patients with refractory cardiogenic shock or cardiac arrest. To contextualize the potential value of ECMO for cardiac indications, we spoke with patients and caregivers with direct experience with the procedure.

Results

We included one systematic review (with 13 observational studies) and two additional observational studies in the clinical review. Compared with traditional CPR for patients with refractory cardiac arrest, ECPR was associated with significantly improved 30-day survival (pooled risk ratio [RR] 1.54; 95% CI 1.03 to 2.30) (GRADE: Very Low) and significantly improved long-term survival (pooled RR 2.17; 95% CI 1.37 to 3.44) (GRADE: Low). Overall, ECPR was associated with significantly improved 30-day favourable neurological outcome in patients with refractory cardiac arrest compared with traditional CPR; pooled RR 2.02 (95% CI 1.29 to 3.16) (GRADE: Very Low). For patients with cardiogenic shock, ECMO was associated with a significant improvement in 30-day survival compared with intra-aortic balloon pump (pooled RR 2.11; 95% CI 1.23 to 3.61) (GRADE: Very Low). Compared with temporary percutaneous ventricular assist devices, ECMO was not associated with improved survival (pooled risk ratio 0.94; 95% CI 0.67 to 1.30) (GRADE: Very Low).

We estimated the incremental cost-effectiveness ratio of ECPR compared with conventional CPR is $18,722 and $28,792 per life-year gained (LYG) for in-hospital and out-of-hospital cardiac arrest, respectively. We estimated the probability of ECPR being cost-effective versus conventional CPR is 93% and 60% at a willingness-to-pay of $50,000 per LYG for in-hospital and out-of-hospital cardiac arrest, respectively. We estimate that publicly funding ECMO in Ontario over the next 5 years would result in additional total costs of $1,673,811 for cardiogenic shock (treating 314 people), $2,195,517 for in-hospital cardiac arrest (treating 126 people), and $3,762,117 for out-of-hospital cardiac arrest (treating 247 people).

The eight patients and family members with whom we spoke had limited ability to assess the impact of ECMO or report their impressions because of their critical medical situations when they encountered the procedure. All had been in hospital with acute hemodynamic instability. In the decision to receive the procedure, participants generally relied on the expertise and judgment of physicians.

Conclusions

For adults treated for refractory cardiac arrest, ECPR may improve survival and likely improves long-term neurological outcomes compared with conventional cardiopulmonary resuscitation. For patients treated for cardiogenic shock, ECMO may improve 30-day survival compared with intra-aortic balloon pump, but there is considerable uncertainty.

For adults with refractory cardiac arrest, ECPR may be cost-effective compared with conventional CPR. We estimate that publicly funding ECMO for people with cardiac arrest and cardiogenic shock in Ontario over the next 5 years would cost about $845,000 to $2.2 million per year.

People with experience of ECMO for cardiac indications viewed it as a life-saving device and expressed gratitude that it was available and able to help stabilize their acute medical condition.

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OBJECTIVE

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of extracorporeal membrane oxygenation for treating adults with cardiac arrest or cardiogenic shock when these conditions are refractory (not responding to standard care). It also evaluates the budget impact of publicly funding extracorporeal membrane oxygenation, and the experiences, preferences, and values of people with lived experience of this procedure.

BACKGROUND

Health Conditions

Cardiac arrest is the abrupt loss of heart function in a person who may or may not have been diagnosed with heart disease. It can come on suddenly, or in the wake of other symptoms.[1]

Cardiogenic shock occurs when the heart is unable to circulate oxygenated (oxygen-rich) blood to vital organs. As a result, cells in the organs stop functioning and cell death may occur. The onset of cardiogenic shock may be due to various conditions, all of which can lead to progressive end-stage heart failure. These include myocardial dysfunction (problems with the heart tissue, such as acute myocardial infarction [heart attack] or myocarditis [inflammation of the heart muscle]), valvular dysfunction (damage to any of the four valves that control the flow of blood between the heart's chambers), or conduction system dysfunction (problems with how electrical impulses travel through the heart and ensure it beats properly).[2]

Cardiac arrest and cardiogenic shock are medical emergencies and require immediate treatment.

Clinical Need and Target Population

Worldwide, the annual incidence of cardiac arrest is 0.1%.[3] Most cardiac arrests occur in out-of-hospital settings and are associated with reduced survival to hospital discharge compared to in-hospital arrests (9.8% vs. 23.8%, respectively [U.S. data]).[3] In-hospital cardiac arrests occur in patients who have already been admitted to hospital due to preceding symptoms and/or other significant comorbidities. In contrast, people with out-of-hospital cardiac arrest typically experience it as a sudden, unexpected event, and they tend to be younger, healthier, and with better prognostic features (characteristics of a patient that can be used to estimate the chance of recovery). Patients who receive timely CPR from bystanders have a greater chance of surviving out-of-hospital cardiac arrest than those who do not.[3]

Acute myocardial infarction accounts for about 80% of cardiogenic shock cases.[4] In people with a type of heart attack known as ST-segment elevation myocardial infarction (in which some heart muscle dies due to a block in blood flow), cardiogenic shock occurs in approximately 5% to 10% of cases, and it occurs in 2% to 3% of people with a non–ST-segment elevation myocardial infarction.[4] (The term *ST-segment elevation* refers to a pattern in the patient's electrocardiogram.) Despite adequate treatment and advances in the availability of early revascularization therapy (to revive the flow of oxygenated blood), cardiogenic shock often leads to multiorgan failure and death. Mortality rates in cardiogenic shock remain as high as 35% to 50%.[4]

Data from the Ontario Myocardial Infarction Database show that the incidence of cardiogenic shock among 311,183 patients who experienced an acute myocardial infarction declined from 3.4% in the years 1992 to 1999 to 2.6% in 2004 to 2008. This decline in cardiogenic shock may be related to the 3% increase between 1992 to 2008 in the number of hospitals capable of performing emergency revascularization.[5] Over the same period, the 1-year mortality rate for cardiogenic shock in Ontario (percentage of patients who died within the year after their cardiogenic shock event) also declined, from 81.1% (1992–1999) to 71.5% (2004–2008).[5] These data are adjusted for age, sex, and comorbidities (acute renal failure, cardiac dysrhythmias, cerebrovascular disease, chronic renal failure, congestive heart failure, diabetes, cancer, and pulmonary edema).

Current Treatment Options

Survival of patients with cardiac arrest, particularly out-of-hospital cardiac arrest, depends on quick administration of cardiopulmonary resuscitation (CPR). Most patients with cardiac arrest refractory (not responsive) to initial conventional CPR will die.[6]

For cardiogenic shock, vasopressor and inotropic drugs (drugs that increase circulation or stimulate the heart muscle) remain the first lines of treatment for cardiogenic shock but frequently offer inadequate support, according to the Canadian Cardiovascular Society guidelines for the management of heart failure.[7]

Short-term mechanical circulatory devices—small, implantable mechanical pumps—are generally used for refractory cardiogenic shock to allow time (a few hours to a few days) to determine the appropriate next steps for the patient. These devices are also known as hemodynamic support devices. They augment the work of a poorly functioning heart to keep oxygenated blood flowing through the body. Examples include[7]:

- Intra-aortic balloon pumps, a device inserted into the aorta (the body's main blood vessel)
- Short-term ventricular assist devices (VADs), which can be surgically implanted (requiring open-heart surgery) or percutaneously implanted (through the skin). Impella and TandemHeart are two of the less invasive, percutaneous VADs

The choice of which temporary mechanical circulatory device to use is based on many factors, including patient characteristics, the degree of desired hemodynamic support, and institutional resources.[7] Mechanical circulatory devices such as durable left ventricular assist devices (LVADs) involve surgical implantation for which many patients may be considered too sick.[7] Although it provides the smallest hemodynamic support, the intra-aortic balloon pump continues to be used in part since it is the easiest to insert in emergency situations.[7]

Short-term mechanical circulatory devices for refractory cardiogenic shock may be used as a bridge to keep the person alive until they either recover, are ready for a longer-term surgically implanted VAD, or are able to have a heart transplant, as appropriate.[8]

Health Technology Under Review

Extracorporeal life support includes a spectrum of mechanical cardiopulmonary support, and one example is extracorporeal membrane oxygenation (ECMO).[9] Like the current treatment options described above, this procedure is a rescue therapy, used in an intensive care setting to

sustain the person's life for a few hours or days, up to a few weeks. It is not a treatment or cure for heart failure; rather, it substitutes for the work of the heart and lungs, allowing them to rest until time or additional procedures help to reverse the problem that caused the heart to fail.

The ECMO procedure uses a life support machine connected to the patient through cannula (tubes) inserted in large veins and arteries in the legs, neck, or chest. The procedure to insert the tubes is called cannulation. The machine pumps the patient's blood to an artificial lung, removing carbon dioxide and adding oxygen, and then back into the body, in a continuous circuit. Extracorporeal membrane oxygenation typically has one of two main configurations: for respiratory support only (no cardiac support required), the procedure involves only the venous system (the veins); this is called venovenous (VV) ECMO. For cardiac support or mixed cardiac and respiratory support, the arterial system is also involved; this is called venoarterial (VA) ECMO. Femoral VA ECMO (in which cannula are inserted in a leg artery) is more common than central VA ECMO (in which cannula are inserted in the chest) for adults who need urgent cardiac support because it can be done rapidly and avoids a sternotomy (breaking the breastbone to access arteries in the chest).[10]

Common indications for VA ECMO are refractory cardiogenic shock in the setting of acute coronary syndrome (e.g., myocardial infarction), acute heart failure, myocarditis, and postcardiotomy syndrome (poor heart function or blood pressure following heart surgery).[11] Absolute contraindications for VA ECMO include disseminated malignancy, unwitnessed cardiac arrest, severe irreversible brain injury or multiorgan failure, severe aortic valve incompetence, or low likelihood of myocardial recovery (unless the person is a candidate for a durable VAD or heart transplant).[11] Relative contraindications (i.e., it is acceptable to use ECMO if the benefits outweigh the risk) include advanced age and bleeding disorders.[11]

This health technology assessment focuses on VA ECMO, which for simplicity we will refer to as ECMO. For people with cardiogenic shock, ECMO may be used as a bridge to either recovery, heart transplantation, or a more permanent surgically implanted VAD (e.g., a long-term LVAD). When used for people with cardiac arrest, the same technology is known as extracorporeal cardiopulmonary resuscitation (ECPR). If the patient does not respond to conventional CPR, ECPR can function as a bridge to recovery of effective cardiac output.[3] In cases in which the cardiac arrest has resulted in a poor neurological outcome (the person has minimal brain function and will die without continuous life support), ECPR may serve as a bridge to consideration for organ donation after life support is removed.

The rescue therapies summarized above represent a continuum of increasing hemodynamic support, from an intra-aortic balloon pump to percutaneous VADs and ECMO.[7] This increased hemodynamic support comes, in general terms, at the expense of more invasive vascular access and greater complication rates, particularly risks of bleeding and leg ischemia (restricted blood flow).[7]

Regulatory Information

Table 1 outlines the four ECMO devices that hold current active licenses in Canada according to the Medical Devices Active License Listing database of Health Canada.[12]

Table 1: Extracorporeal Membrane Oxygenation Devices for Cardiac Indications With Active Licences in Canada

Device (Manufacturer)	Licence No.	Device Class	Approved Indication(s)
CentriMag Extracorporeal Blood Pumping System (Thoratec Switzerland GMBH)	71443	3	Short-term extracorporeal cardiopulmonary bypass or cardiopulmonary support. Also for use in extracorporeal circulatory support systems used during the performance of procedures not requiring complete cardiopulmonary bypass
Extracorporeal Life Support Sets (includes Rotaflow pump) (Maquet Cardiopulmonary GMBH)	92678	3	Suitable for both extracorporeal, pulmonary support, and cardiovascular support, and for simultaneous cardiovascular and pulmonary support
Rotaflow Cardio Pulmonary Bypass Centrifugal Pump (Maquet Cardiopulmonary GMBH)	65399	3	Propels blood in a cardiopulmonary bypass circuit
Cardiohelp-I (Maquet Cardiopulmonary GMBH)	86641	3	Drive, control, monitor, and record an extracorporeal circulation

Source: Health Canada, Medical Devices Active License Listing database.[12]

Ontario, Canadian, and International Context

In Ontario, ECMO is currently used in several centres around the province. Physician fees are covered under a surgical fee code and includes "cannulating and decannulating, by any method, heart, vein and/or artery and repair of vessels."[13] The fee code does not stipulate specific medical indications for which ECMO is covered. Public funding for other aspects related to the provision of ECMO is generally felt to be insufficient to cover costs.

According to the Canadian Cardiovascular Society, there is a paucity of data comparing ECMO with other devices for cardiac indications.[7] Meanwhile, interest in this technology has been growing rapidly. The Extracorporeal Life Support Organization, an international voluntary registry, reports that the overall number of adults worldwide who underwent ECMO for cardiac indications increased 1,180% in the last decade, from fewer than 200 between 1997 and 2007 to more than 2,000 to date.[14] The number of ECMO centres, which increased by 15% (from 115 to 131) from 1996 to 2006, rose 133% (from 131 to 305) between 2006 and 2016.[14]

Reasons behind the international increase in the use of ECMO in cardiology, according to the Journal of the American College of Cardiology Scientific Expert Panel, include the following[14]:

- Availability of durable membranes and portable circuits
- Ability of ECMO to provide left, right, and biventricular support
- Ease of implantation in a catheterization laboratory or at the bedside
- Increased familiarity with the technology by cardiologists and surgeons
- The need for a short-term bridge to transplantation or mechanical support
- Progress in durable (long-term) mechanical circulatory support devices, which allow ECMO to be used as a bridge to LVAD

Interest in ECMO for cardiac indications is growing in Ontario, and therefore this report aims to provide an updated assessment of this technology. The use of ECMO for infants and children with cardiac indications has also been studied; however, we have restricted our evaluation to its use in adults.

Expert Consultation

We engaged with experts in the specialty areas of critical care and cardiology to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD # 42018117477), available at https://www.crd.york.ac.uk/PROSPERO.

CLINICAL EVIDENCE

Research Questions

- What are the effectiveness and safety of extracorporeal cardiopulmonary resuscitation (ECPR) for the treatment of adults with cardiac arrest that is refractory to conventional cardiopulmonary resuscitation (CPR)?
- What are the effectiveness and safety of venoarterial extracorporeal membrane oxygenation (ECMO) for the treatment of adults with cardiogenic shock that is refractory to conventional medical management?

Methods

Clinical Literature Search

We performed a clinical literature search on September 20, 2018, to retrieve studies published from January 1, 2010, until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[15]

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. See Appendix 1 for the literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from 2010 to present
- Systematic reviews, health technology assessments, randomized controlled trials, observational studies

Exclusion Criteria

- Animal and in vitro studies
- Editorials, commentaries, case reports, conferences abstracts, letters

Participants

- Adults (≥ 18 years) with cardiac arrest that is refractory to conventional cardiopulmonary resuscitation
- Adults (≥ 18 years) with cardiogenic shock that is refractory to conventional medical management: drugs, mechanical support (e.g., intra-aortic balloon pump, percutaneously inserted temporary ventricular support device [e.g., Impella], surgically implanted temporary ventricular support devices)

Interventions

Inclusion Criteria

- Extracorporeal cardiopulmonary resuscitation
- Venoarterial extracorporeal membrane oxygenation used as a bridge to recovery, heart transplantation, or implantation of longer-term surgically implanted devices

Exclusion Criteria

- Venovenous extracorporeal membrane oxygenation

Comparators

- For refractory cardiac arrest: standard care, e.g., conventional CPR
- For refractory cardiogenic shock: standard care, i.e., drugs, temporary mechanical support (e.g., intra-aortic balloon pump, percutaneously inserted temporary ventricular support devices, surgically implanted ventricular assist devices [VAD])

Outcomes of Interest

For both cardiogenic shock and cardiac arrest:

- Survival, 30-day and long-term
- Favourable neurological outcome (i.e., absence of severe brain damage), 30-day and long-term
- Successfully weaned or bridged to permanent VAD or heart transplant
- Safety/complications/adverse events, short- and long-term
- Quality of life, short- and long-term
- Time in intensive care
- Length of stay in hospital

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[16] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, and whether the study compared two or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower limits [for scales], and time points at which the outcomes were assessed)

Statistical Analysis

We performed a quantitative synthesis of the individual studies using Review Manager, version 5.[17]

We expressed summary measures as the risk ratio for dichotomous data using the Mantel-Haenszel method. We assessed statistical heterogeneity using the I^2 statistic in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*: low heterogeneity (0%–40%), moderate (30%–60%), substantial (50%–90%), and considerable (75%–100%).[18] Results were pooled using a random-effects model, and we examined graphs of the forest plots. A *P* value of .05 or less was considered statistically significant for the overall effect estimate.

We conducted subgroup analyses for outcomes of patients who received ECPR for in-hospital versus out-of-hospital cardiac arrest.

Critical Appraisal of Evidence

We assessed risk of bias using the Risk of Bias in Systematic Reviews (ROBIS) tool for systematic reviews and the Risk of Bias Among Nonrandomized Trials (ROBINS-I) tool for observational studies. (Appendix 2).[19,20]

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[21] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence (Appendix 2).

Results

Clinical Literature Search

The literature search yielded 4,028 citations published between January 1, 2010, and September 20, 2018, after removing duplicates. We identified 19 studies (5 systematic reviews and 14 nonrandomized controlled trials) that initially met our inclusion criteria. No randomized controlled trials met our inclusion criteria. We included one systematic review of 13 observational studies—selected for its low risk of bias, comprehensiveness, and recency—as

well as two additional observational studies. See Appendix 3 for a list of selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

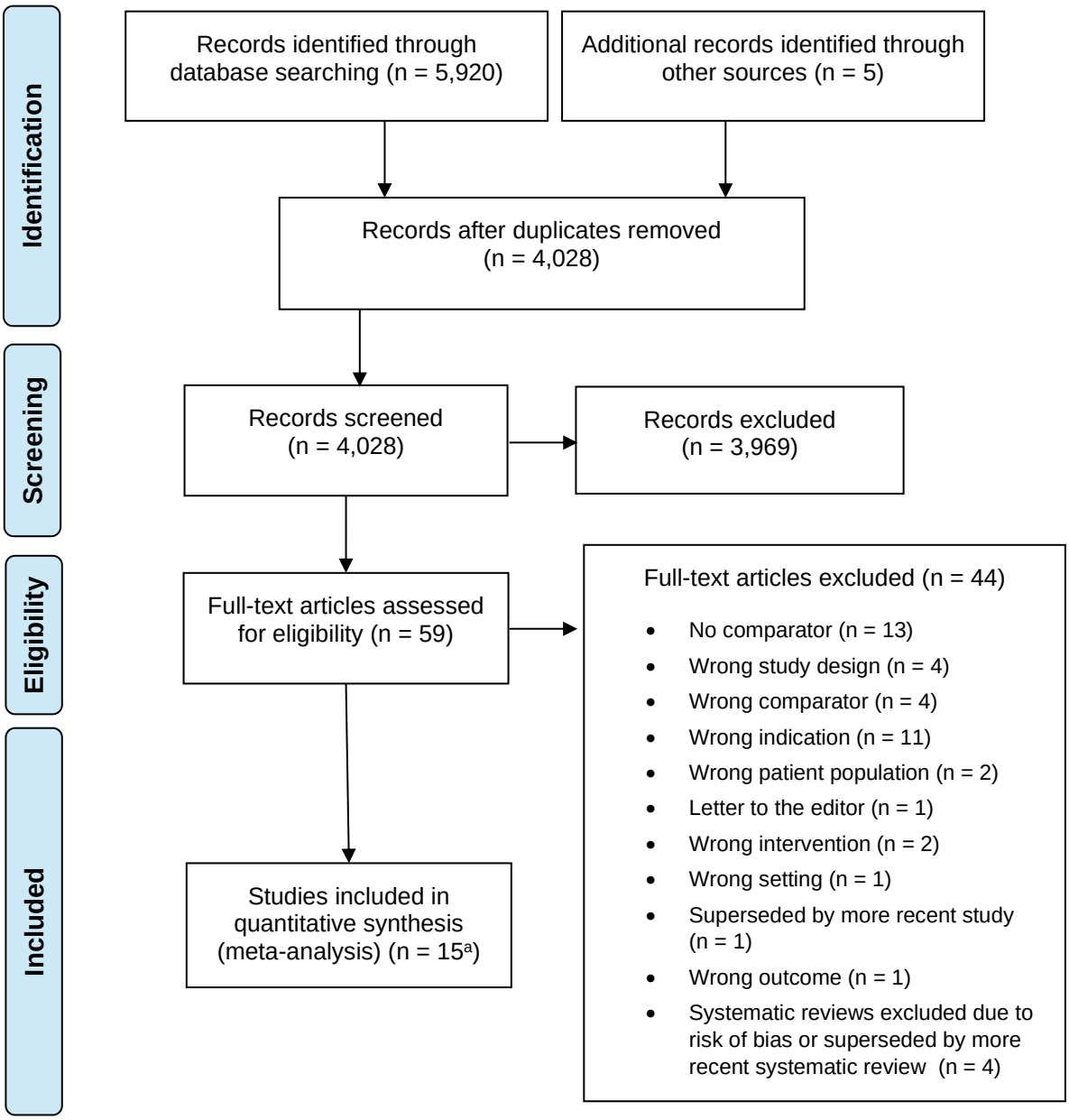

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy
Source: Adapted from Moher et al, 2009.[22]
[a]Includes 13 observational studies from one systematic review (Ouweneel et al, 2016[8]) plus 2 recent observational studies.

Systematic Reviews

Five systematic reviews initially met our inclusion criteria.[8,23,24] The reviews were published between 2016 and 2017 and examined the effectiveness of ECMO for the treatment of cardiac arrest (ECPR)[23,24], or both cardiac arrest and cardiogenic shock.[8,25,26] Overall, the quality of the five systematic reviews varied (Appendix 2, Table A1). Using the ROBIS tool, we rated three systematic reviews as having a low risk of bias.[8,23,24] Two systematic reviews were rated as having a high risk of bias in at least one category,[25,26] and we therefore excluded them from the analysis.

The systematic review by Ouweneel et al[8] examined the effectiveness of extracorporeal membrane oxygenation for the treatment of both cardiac arrest (ECPR) and cardiogenic shock (ECMO) and was the publication that conducted the most recent literature search (December 2015). The systematic review by Ouweneel et al[8] also included studies that were incorporated in the systematic reviews by Wang et al[24] and Kim et al[23], which only focused on the effectiveness of ECMO for cardiac arrest (ECPR). Therefore, we used the systematic review by Ouweneel et al as a source of study identification, and extracted the data and quality assessment reported within.

Observational Studies

The systematic review by Ouweneel et al[8] identified 13 observational studies. In addition to these 13 studies, our literature search identified two more recent nonrandomized studies[27,28] published after the literature search cut-off date in the systematic review by Ouweneel et al.[8]

Appendix 4, Tables A5 and A6, present characteristics of the studies included by Ouweneel et al,[8] and Table A7 presents characteristics of the two more recent studies we identified.

Risk of Bias in the Included Studies

Ouweneel et al[8] assessed the overall quality of the studies as low with a high risk of bias, using a modified version of the Newcastle–Ottawa Quality Assessment Scale for Cohort studies.[29] We assessed the overall quality of the studies by Choi et al[28] and Mohite et al[27] using the ROBINS-I tool and rated the quality of both as low (Appendix 2, Table A2).

Extracorporeal Cardiopulmonary Resuscitation for the Treatment of Adults With Cardiac Arrest

Thirty-Day Survival

Ouweneel et al[8] reported a meta-analysis of eight observational studies[30-37] assessing 30-day survival in patients with cardiac arrest treated with ECPR compared with traditional CPR. (For study details, see Appendix 4, Table A5). Overall, the authors reported the quality of all eight studies was low with a high risk of bias based on the Newcastle–Ottawa Quality Assessment Scale for Cohort Studies.[8]

The authors also conducted a subgroup meta-analysis of five studies that used propensity score matching.[30,32,34,36,38] Propensity score matching is a statistical procedure to adjust for confounding variables and reduce treatment selection bias, a common issue with observational studies.[39] For example, when determining a course of treatment, a physician may choose to pursue more aggressive therapies only in patients with advanced disease; an observational

study comparing the effectiveness of two treatments is going to be confounded by the fact that patients receiving aggressive therapies are likely to have worse prognoses and are therefore not be comparable to those receiving less aggressive therapies.[39]

In addition, after the publication by Ouweneel et al,[8] Choi et al[28] published a retrospective cohort study with propensity score matching to compare survival outcomes in patients who received ECPR versus conventional CPR (see Appendix 4, Table A7).

We therefore added the study by Choi et al[28] to the five cohort studies[30,32,34,36,38] included in Ouweneel et al[8] and meta-analyzed the data. Figure 2 presents results of our meta-analysis of six cohort studies that used propensity score matching. In our analysis, we both separated and pooled the data on in-hospital and out-of-hospital cardiac arrest; Ouweneel et al[8] had pooled them. Overall, ECPR was associated with significantly improved 30-day survival in patients with refractory cardiac arrest compared with traditional CPR; pooled risk ratio 1.54 (95% confidence interval [CI] 1.03 to 2.30). When we separately analyzed in- and out-of-hospital cardiac arrest, ECPR was associated with significantly improved 30-day survival for patients with in-hospital cardiac arrest (risk ratio 2.03 [95% CI 1.30 to 3.18]), but not for patients with out-of-hospital cardiac arrest (risk ratio 1.18 [95% CI 0.71 to 1.97]) (Figure 2).

We rated the certainty of evidence for this outcome as very low, downgrading for inconsistency (discrepancy in results for in-hospital versus out-of-hospital cardiac arrest) (Appendix 2, Table A3).

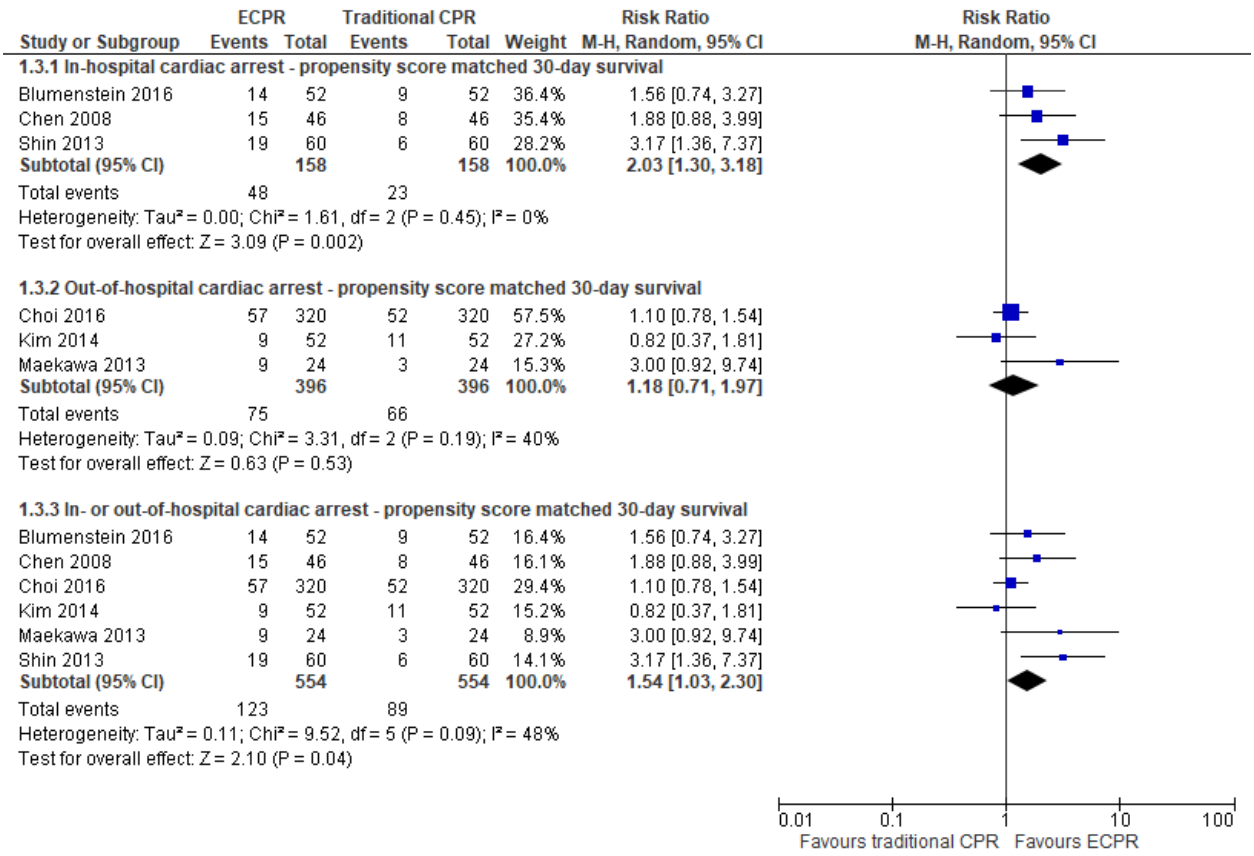

Figure 2: 30-Day Survival in Adults With Cardiac Arrest (Within Studies Using Propensity Score Matching)

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; M-H, Mantel-Haenszel.

Sources: Studies identified from the systematic review by Ouweneel et al, 2016,[8] and from our primary literature search: Blumenstein et al, 2016[38]; Chen et al, 2008[30]; Choi et al, 2016[28]; Kim et al, 2014[32]; Maekawa et al, 2013[34]; Shin et al, 2013.[36]

Long-Term Survival

Ouweneel et al[8] reported a meta-analysis of eight observational studies[30-32,34-38] assessing long-term survival in patients with cardiac arrest treated with ECPR compared with traditional CPR. (See Appendix 4, Table A5, for study details.) Follow-up duration ranged from 3 months to 2 years.

The authors also meta-analyzed a subgroup of five studies that used propensity score matching.[30,32,34,36,38] We did not identify any additional recent studies reporting long-term survival. Ouweneel et al[8] pooled in-hospital and out-of-hospital cardiac arrest; we meta-analyzed the data for the two conditions both separately and pooled (Figure 3).

Overall, ECPR was associated with significantly improved long-term survival in patients with refractory cardiac arrest compared with traditional CPR; pooled risk ratio = 2.17 (95% CI 1.37 to 3.44). When we analyzed in- and out-of-hospital cardiac arrest separately, ECPR was associated with significantly improved long-term survival for patients with in-hospital cardiac arrest (risk ratio = 1.99 [95% CI 1.16 to 3.41]) and patients with out-of-hospital cardiac arrest (risk ratio = 2.74 [95% CI 1.13 to 6.67]) (Figure 3).

We rated the certainty of evidence for this outcome as low (Appendix 2, Table A3).

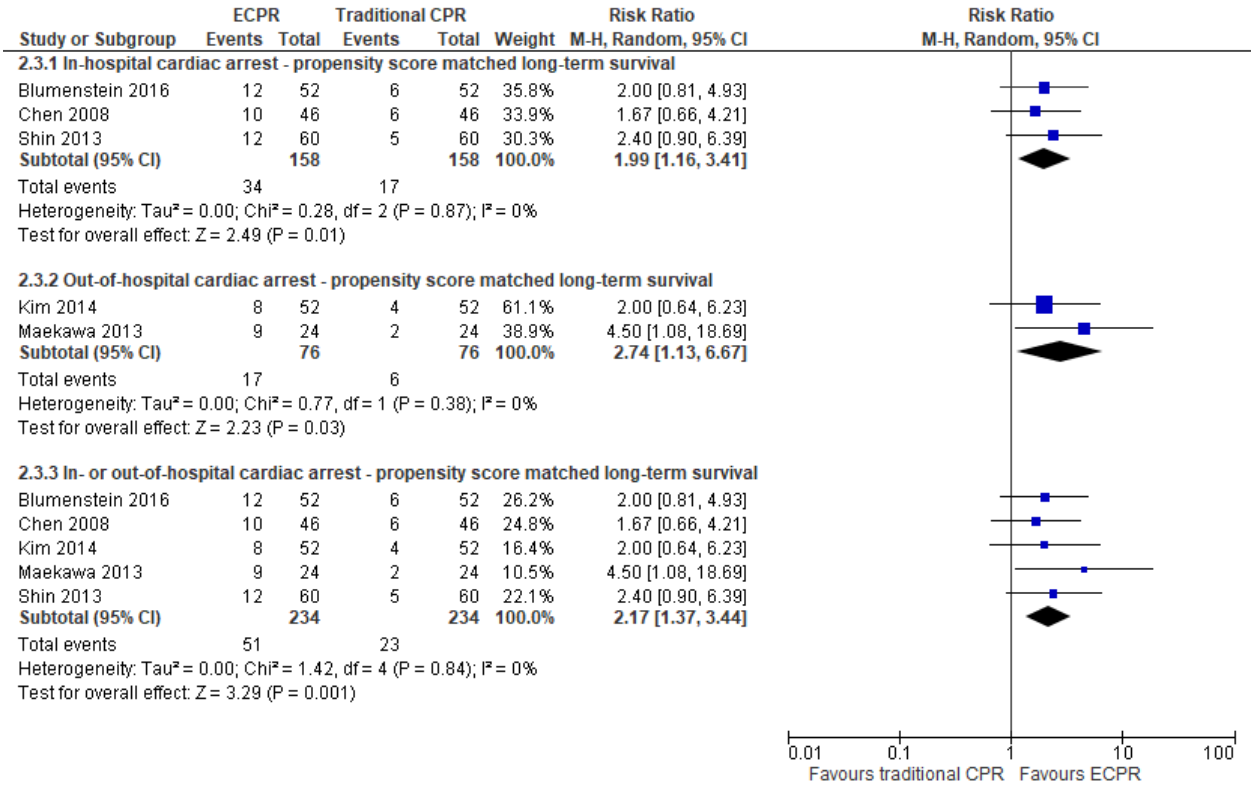

Figure 3: Long-Term Survival in Adults With Cardiac Arrest (Within Studies Using Propensity Score Matching)

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; M-H, Mantel-Haenszel.

Sources: Studies identified from the systematic review by Ouweneel et al, 2016,[8] and from our primary literature search: Blumenstein et al, 2016[38]; Chen et al, 2008[30]; Kim et al, 2014[32]; Maekawa et al, 2013[34]; Shin et al, 2013.[36]

Thirty-Day Favourable Neurological Outcome

Ouweneel et al[8] reported a meta-analysis of five cohort studies[30,32,35-37] assessing 30-day favourable neurological outcome in patients with cardiac arrest treated with ECPR compared with traditional CPR. Neurological status was considered favourable when reported as either Pittsburgh Cerebral Performance Category (CPC) score of 1 or 2, or a Modified Glasgow Outcome Score (MGOS) of 4 or higher.[8]

The authors also meta-analyzed a subgroup of four studies that used propensity score matching.[30,32,36,38] We identified a retrospective cohort study with propensity score matching by Choi et al[28] that reported on 30-day favourable neurological outcome. We added that study to the four cohort studies included in Ouweneel et al[8] and meta-analyzed the data. Figure 4 presents results for in-hospital and out-of-hospital cardiac arrest, separately and pooled.

Overall, ECPR was associated with significantly improved 30-day favourable neurological outcome in patients with refractory cardiac arrest compared with traditional CPR; pooled risk ratio = 2.02 (95% CI 1.29 to 3.16). When in- and out-of-hospital cardiac arrest were analyzed separately, ECPR was associated with significantly improved 30-day favourable neurological

outcome for patients with in-hospital cardiac arrest (risk ratio 2.18 [95% CI 1.24 to 3.81]), but not for patients with out-of-hospital cardiac arrest (risk ratio 2.61 [95% CI 0.56 to 12.20]) (Figure 4).

We rated the certainty of evidence for this outcome as very low, downgrading due to inconsistency (discrepancy in results for in-hospital versus out-of-hospital cardiac arrest) (Appendix 2, Table A3).

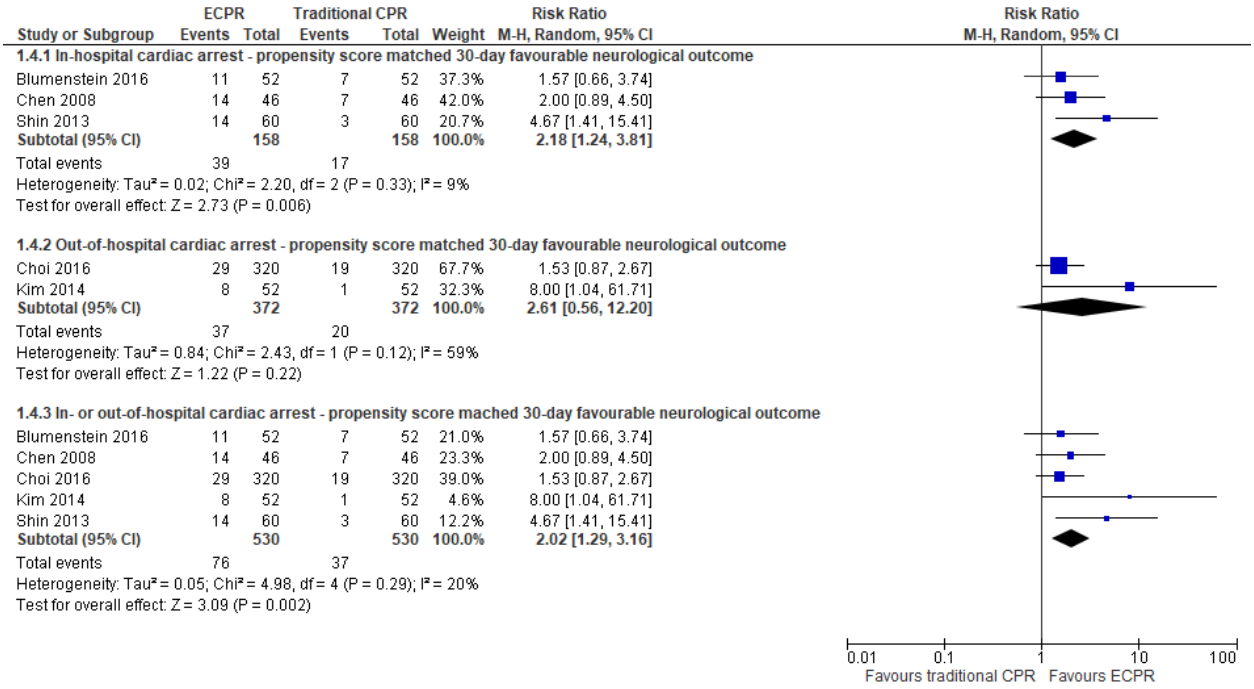

Figure 4: 30-Day Favourable Neurological Outcome in Adults With Cardiac Arrest (Within Studies Using Propensity Score Matching)

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; M-H, Mantel-Haenszel.

Sources: Studies identified from the systematic review by Ouweneel et al, 2016,[8] and from our primary literature search: Blumenstein et al, 2016[38]; Chen et al, 2008[30]; Choi et al, 2016[28]; Kim et al, 2014[32]; Shin et al, 2013.[36]

Long-Term (> 30 Days) Favourable Neurological Outcome

Ouweneel et al[8] reported a meta-analysis of six cohort studies[30,32,34-37] assessing long-term favourable neurological outcome in patients with cardiac arrest treated with ECPR compared with traditional CPR.

The authors also meta-analyzed a subgroup of five studies using propensity score matching.[30,32,34,36,38] We did not identify any recent studies with long-term favourable neurological outcome to add to the meta-analysis by Ouweneel et al.[8] Figure 5 shows results of the meta-analysis of propensity score matched studies. Ouweneel et al[8] pooled in-hospital and out-of-hospital cardiac arrest; for this review, we also analyzed these two conditions separately.

Overall, ECPR was associated with significantly improved long-term favourable neurological outcome in patients with refractory cardiac arrest compared with traditional CPR; pooled risk ratio = 2.86 (95% CI 1.64 to 5.01). Similarly, when we analyzed in- and out-of-hospital cardiac arrest separately, ECPR was associated with significantly improved long-term favourable

neurological outcome for patients with in-hospital cardiac arrest (risk ratio 2.50 [95% CI 1.33 to 4.71]), and out-of-hospital cardiac arrest (risk ratio 4.64 [1.41 to 15.25]) (Figure 5).

We rated the certainty of evidence for this moderate, upgrading the certainty since the risk ratio was greater than 2 and the lower confidence limit was greater than 1.5. (Appendix 2, Table A3).

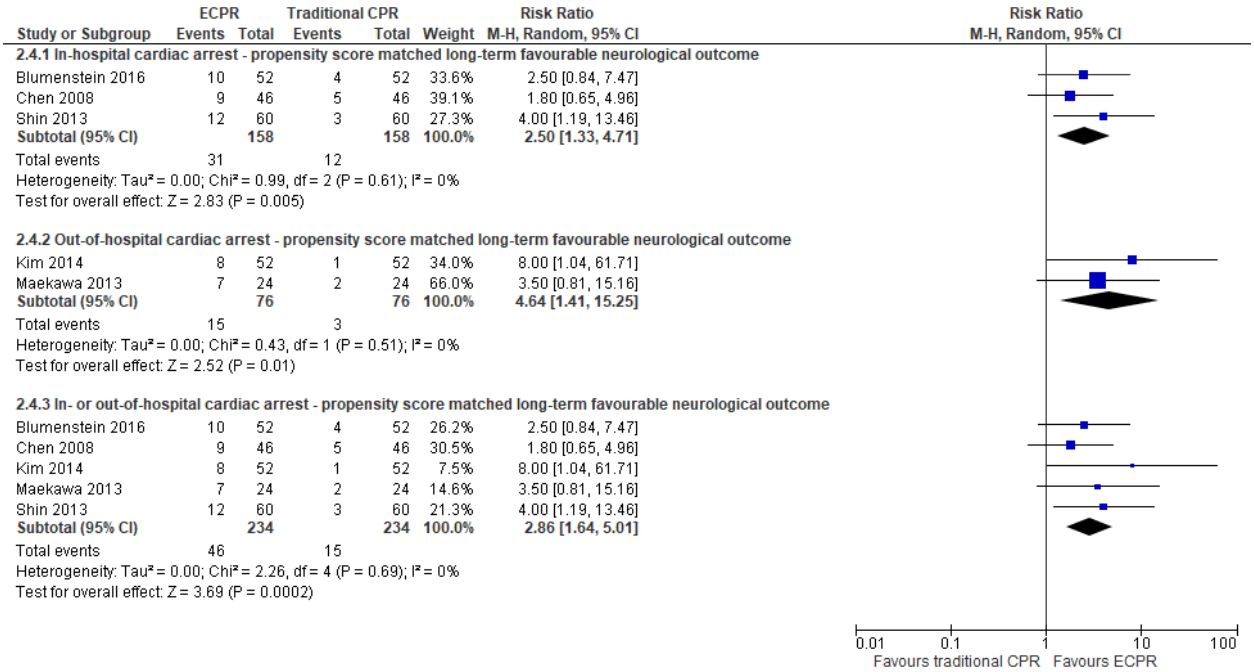

Figure 5: Long-Term Favourable Neurological Outcome in Adults With Cardiac Arrest (Within Studies Using Propensity Score Matching)

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; M-H, Mantel-Haenszel.

Sources: Studies identified from the systematic review by Ouweneel et al, 2016,[8] and from our primary literature search: Blumenstein et al, 2016[38]; Chen et al, 2008[30]; Kim et al, 2014[32]; Maekawa et al, 2013[34]; Shin et al, 2013.[36]

Successfully Weaned or Bridged to Long-Term Ventricular Assist Device or Heart Transplant

Very few studies included in the systematic review by Ouweneel et al[8] reported whether patients were successfully weaned off the machine, were bridged to a long-term VAD, or received a heart transplant. In a non–propensity score matched analysis, Chen et al[30] found a significant difference in the number of patients treated with ECPR who received a long-term VAD or a heart transplant compared with patients treated with conventional CPR (3 [5.1%] vs. 0 [0%], P = .04, or 5 [8.5%] vs. 0 [0%], P = .004, respectively). Chen et al[30] also reported 29 out of 59 patients (49.2%) were weaned off ECPR.

The more recent cohort study by Choi et al[28] did not report this outcome.

We rated the certainty of evidence for this outcome as very low, downgrading due to risk of bias (Appendix 2, Table A3).

Complications

In the systematic review by Ouweneel et al,[8] the authors stated complication rates were very poorly reported. One of the studies that used propensity score matching reported the complications shown in Table 2.[38] Overall, patients who received ECPR had significantly more complications related to malperfusion (restricted blood flow) of the leg (*P* = .02) and bleeding or hematoma with need for transfusion (*P* = .03), compared with those receiving traditional CPR.

Table 2: Complications for Adults With Cardiac Arrest Treated With Extracorporeal or Traditional Cardiopulmonary Resuscitation

Complication	ECPR (N = 52) n (%)	Traditional CPR (N = 52) n (%)	*P* Value
Malperfusion of the leg	9 (17.3)	1 (1.9)	.02
Bleeding or hematoma with need for transfusion	17 (32.7)	7 (13.5)	.03
Sepsis/systemic inflammatory response syndrome	4 (7.7)	5 (9.6)	.87
Acute kidney failure	1 (1.9)	5 (9.6)	.20

Abbreviations: CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation.
Source: Data reported by Blumenstein et al, 2016.[38]

The additional study by Choi et al[28] comparing cardiac arrest patients treated with ECPR or conventional CPR did not report complications.

We rated the certainty of evidence for this outcome as low (Appendix 2, Table A3).

Quality of Life

None of the studies that met the inclusion criteria for this systematic review reported this outcome.

Time in Intensive Care

None of the studies that met the inclusion criteria for this systematic review reported this outcome.

Length of Stay

Although Ouweneel et al[8] did not report this outcome, one of their included studies reported no significant difference in hospital stay (non–propensity score matched analysis) for patients who received ECPR (median 12 days [range 1–93]) compared with conventional CPR (median 12 days [range 1–174], *P* = .44).[30]

We rated the certainty of evidence for this outcome as very low, downgrading due to risk of bias (Appendix 2, Table A3).

Extracorporeal Membrane Oxygenation for the Treatment of Adults With Cardiogenic Shock

Thirty-Day Survival

Ouweneel et al[8] also reported a meta-analysis of four cohort studies[40-43] assessing 30-day survival in patients with cardiogenic shock treated with ECMO compared with either intra-aortic balloon pump or percutaneous VADs (e.g., Impella, TandemHeart). Appendix 4, Table A6, provides details of these four studies. Overall, the authors reported the quality of the studies was low with a high risk of bias based on the Newcastle Ottawa Quality Assessment Scale for Cohort Studies.[8]

In addition, we included a retrospective cohort study by Mohite et al[27] published after the literature search conducted by Ouweneel et al[8] (see Appendix 4, Table A7, for study characteristics). The comparator in the study by Mohite et al,[27] which looked at outcomes in patients with postcardiotomy cardiogenic shock, was a temporary nonpercutaneous VAD, such as a left ventricular assist device (LVAD).

We added the study by Mohite et al[27] to the four studies included in Ouweneel et al[8] and undertook a meta-analysis. None of the studies performed a propensity score matched analysis. Figure 6 shows results of this meta-analysis.

The pooled risk ratio comparing ECMO with intra-aortic balloon pump (two studies[40,41]) was 2.11 (95% CI 1.23 to 3.61), indicating ECMO was associated with a significant improvement in 30-day survival compared to intra-aortic balloon pump in patients with cardiogenic shock. For ECMO compared with temporary percutaneous VADs (e.g., Impella or TandemHeart; two studies[42,43]), the pooled risk ratio was 0.94 (95% CI 0.67 to 1.30), indicating ECMO was not associated with significantly improved survival compared with percutaneous VADs. Compared with temporary nonpercutaneous VADs (e.g., left ventricular assist devices), ECMO was associated with a significant decrease in 30-day survival (one study[27]) in patients with cardiogenic shock (risk ratio 0.38 [95% CI 0.16 to 0.86]).

We rated the certainty of evidence for this outcome as very low, downgrading due to risk of bias (Appendix 2, Table A4).

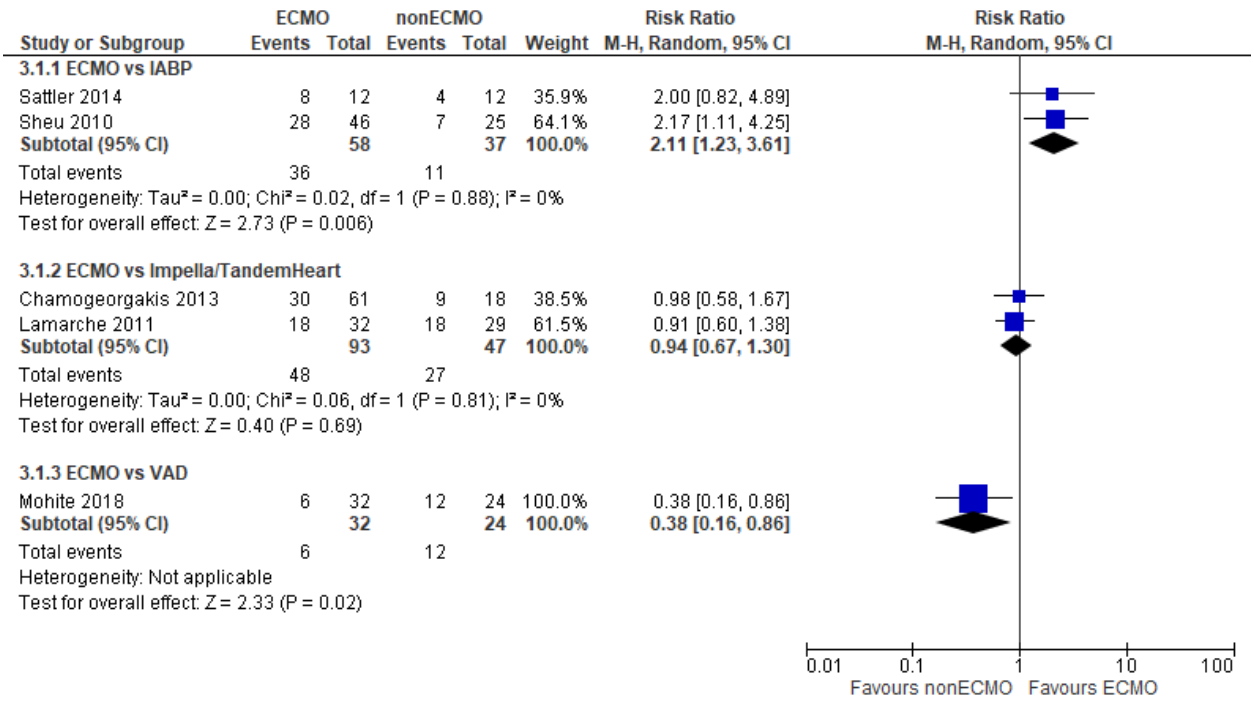

Figure 6: 30-Day Survival in Adults With Cardiogenic Shock

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; M-H, Mantel-Haenszel; VAD, ventricular assist device.

Sources: Studies identified from the systematic review by Ouweneel et al, 2016,[8] and from our primary literature search: Chamogeorgakis et al, 2013[42]; Lamarche et al, 2011[44]; Mohite et al, 2018[27]; Sattler et al, 2014[40]; Sheu et al, 2010.[41]

Long-Term Survival (> 30 Days)

None of the studies included in the systematic review by Ouweneel et al[8] reported long-term survival in patients with cardiogenic shock.

The only study providing survival data beyond 30 days in patients with cardiogenic shock was the cohort study comparing ECMO with temporary nonpercutaneous VADs by Mohite et al.[27] Table 3 displays the survival data at 6-month, 1-year, and 4-year follow-up. Overall, cumulative survival in long-term follow-up was significantly better in patients who received VADs compared with ECMO (*P* = .01, log rank Mantel-Cox).

We rated the certainty of evidence for this outcome as very low, downgrading due to risk of bias (Appendix 2, Table A4).

Table 3: Survival at Long-Term Follow-Up for Adults With Cardiogenic Shock Treated With Extracorporeal Membrane Oxygenation or Nonpercutaneous Ventricular Assist Devices

	Survival	
Follow-Up	ECMO (N = 32) n (%)	Nonpercutaneous VAD (N = 24) n (%)
6 months	6 (18.8)	10 (41.7)
1 year	5 (15.6)	9 (37.5)
4 years	5 (15.6)	9 (37.5)

Abbreviations: ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.
Source: Data reported by Mohite et al, 2018.[27]

Thirty-Day Favourable Neurological Outcome

No studies in the systematic review by Ouweneel et al[8] reported 30-day favourable neurological outcome of patients with cardiogenic shock treated with ECMO compared with intra-aortic balloon pump or temporary percutaneous VADs.

The cohort study by Mohite et al,[27] which compared ECMO with temporary nonpercutaneous VADs in patients with postcardiotomy cardiogenic shock, also did not report 30-day favourable neurological outcome.

Long-Term Favourable Neurological Outcome

No studies of patients with cardiogenic shock treated with ECMO compared with intra-aortic balloon pump or Impella/TandemHeart reported long-term favourable neurological outcome in the systematic review by Ouweneel et al.[8]

The cohort study by Mohite et al[27] also did not report long-term favourable neurological outcome.

Successfully Weaned or Bridged to Long-Term Ventricular Assist Device or Heart Transplant

Lamarche et al[44] and Chamogeorgakis et al[42] reported no significant difference in the proportion of people successfully weaned off ECMO, bridged to permanent VADs, or received a heart transplant among patients who received ECMO versus a percutaneous VAD for the treatment of cardiogenic shock (Table 4).

Table 4: Weaning and Bridging to Permanent Ventricular Assist Devices or Transplant Outcomes for Adults With Cardiogenic Shock and Treated With Extracorporeal Membrane Oxygenation or Percutaneous Ventricular Assist Devices

Outcome	ECMO n (%)	VAD n (%)	*P* Value
Data reported by Lamarche et al, 2011[44]	(N = 32)	(N = 29; Impella)	
Weaned	15 (46.9)	12 (41.4)	.67
Bridge to permanent VAD	6 (18.8)	8 (27.6)	.41
Bridge to transplant	3 (9.4)	0 (0)	.09
Data reported by Chamogeorgakis et al, 2013[42]	(N = 61)	(N = 18; Impella/TandemHeart)	
Weaned	12 (19.7%)	6 (33.3%)	.34
Bridge to long-term support or transplant	19 (31.1%)	5 (27.8%)	.99

Abbreviations: ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.

Mohite et al[27] reported significantly more patients with a temporary nonpercutaneous VAD underwent "successful weaning/upgrade" compared with ECMO patients (VAD 13 [54%] vs. ECMO 9 [28%], *P* = .04). That study found no significant difference between patient groups in terms of conversion to another mechanical circulatory support device (ECMO 4 [13%] vs. VAD 3 [13%], *P* = 1.00).

We rated the certainty of evidence for this outcome as very low, downgrading due to risk of bias (Appendix 2, Table A4).

Complications

One study included in the systematic review by Ouweneel et al[8] reported complications for patients with cardiogenic shock treated with ECMO compared with percutaneous VADs.[42] Chamogeorgakis et al[42] found no significant difference in limb complications between patients who received ECMO (8/61, 13.1%) compared with percutaneous VADs (4/18, 22.2%, *P* = .45).

Mohite et al[27] reported complications for patients with postcardiotomy cardiogenic shock who received ECMO compared with a nonpercutaneous VAD (Table 5). There was significantly more septic shock (*P* = .01) and systemic inflammatory response (*P* < .001) in patients treated with ECMO compared with VADs (Table 5).[27]

We rated the certainty of evidence for this outcome as very low, downgrading due to risk of bias (Appendix 2, Table A4).

Table 5: Complications in Adults Receiving Extracorporeal Membrane Oxygenation or Ventricular Assist Devices for Postcardiotomy Cardiogenic Shock

Outcome	ECMO (N = 32) n (%)	VAD (N = 24) n (%)	*P* Value
Culture positive infection	9 (28)	5 (21)	.53
Septic shock	9 (28)	1 (4)	.01
Systemic inflammatory response	16 (50)	1 (4)	< .001
Bleeding	23 (74)	16 (67)	.54
Tamponade	10 (31)	3 (13)	.10
Limb ischemia	5 (16)	0 (0)	.06
Stroke	1 (3)	1 (4)	1.00
Hepatic failure	15 (47)	12 (50)	.82
Renal failure	22 (69)	12 (50)	.16

Abbreviations: ECMO, extracorporeal membrane oxygenation; VAD, ventricular assist device.
Source: Data reported by Mohite et al, 2018.[27]

Quality of Life

None of the studies that met the inclusion criteria for this systematic review reported this outcome.

Time in Intensive Care

The systematic review by Ouweneel et al[8] did not report this outcome, nor did any of their included studies.

Mohite et al[27] reported no significant difference in time in intensive care for patients with postcardiotomy cardiogenic shock treated with ECMO or nonpercutaneous VADs (median 8 days [interquartile range 3–20] vs. median 12 days [interquartile range 4–30], respectively, *P* = .26).

We rated the certainty of evidence for this outcome as very low, downgrading due to risk of bias (Appendix 2, Table A4).

Length of Stay

The systematic review by Ouweneel et al[8] did not report this outcome, nor did any of their included studies.

Mohite et al[27] reported no significant difference in length of hospital stay for patients with postcardiotomy cardiogenic shock treated with ECMO or temporary nonpercutaneous VADs (median 8 days [interquartile range 3–20] vs. median 24 days [interquartile range 4–67], respectively, *P* = .19).

We rated the certainty of evidence for this outcome as very low, downgrading due to risk of bias (Appendix 2, Table A4).

Ongoing Studies

We are aware of 18 ongoing clinical trials and 11 ongoing health technology assessments, listed in Appendix 6, that have potential relevance to this review.

Discussion

For both in- and out-of-hospital refractory cardiac arrest, ECPR was associated with a 10% increase in survival and a 10% increase in favourable neurological outcome at 30 days compared with traditional CPR. ECPR was also associated with increased survival (11%) and favourable neurological outcome (13%) in the long term (beyond 30 days).

In adults with cardiogenic shock, ECMO has been associated with improved 30-day survival (33%) compared with intra-aortic balloon pump, but not when compared with percutaneous VADs (Impella or TandemHeart). One study compared temporary nonpercutaneous implanted VADs with ECMO and found VADs were associated with significantly higher 30-day and long-term survival.[27]

Strengths and Limitations

Cardiac Arrest

In an attempt to reduce treatment selection bias, studies included in this health technology assessment used propensity score analyses to compare patients with refractory cardiac arrest treated with ECPR or conventional CPR. Although useful for statistically adjusting for confounding variables, this method has limitations. The key assumption underlying such analyses is that, because the propensity score is estimated using observed baseline covariates, patients with equal propensity scores will have similar baseline covariate values and therefore be at similar risk for the outcome of interest.[39] Another important assumption necessary for propensity score analysis is that there are no unmeasured confounders; i.e., it is assumed all factors that might affect treatment assignment and/or the outcome of interest were observed and included in the calculation of the propensity score. However, the presence of an unmeasured confounder can lead to biased results.[39] Other limitations to propensity score analyses include potential errors used in the model to estimate the propensity score. As well, propensity score analyses work better in larger sample sizes, whereas our included studies had sample sizes of 92 to 640, which are generally considered to be relatively small.

In many of the cardiac arrest studies, the decision to use ECPR was based on the judgment or discretion of the attending physician. In their systematic review, Ouweneel et al[8] stated the overall baseline characteristics differed for the ECPR and CPR treatment groups (before the authors analysed the propensity score matched studies separately).[8] For example, cardiac arrest patients who received ECPR tended to be younger, had experienced an acute myocardial infarction, and were more likely to undergo primary percutaneous coronary interventions—all factors known to be associated with increased survival.[8] Also, sicker patients may have been considered too ill to receive ECPR.[8] In general, it is difficult to distinguish the effect of ECPR and the effect of the bias and confounding inherent to cohort studies.

In addition to differences in baseline characteristics, Ouweneel et al[8] noted that differences in the treatment of cardiac arrest patients may have influenced the results. For example, patients treated with ECPR were more likely to be revascularized (have a procedure to restore blood flow, such as bypass surgery or angioplasty).[8]

In contrast to the systematic review by Ouweneel et al,[8] we conducted separate analyses for in-hospital and out-of-hospital cardiac arrest. Although the cardiac arrest cohort studies had different inclusion criteria (e.g., in-hospital cardiac arrest, out-of-hospital cardiac arrest, witnessed or non-witnessed cardiac arrest, and differing durations of cardiopulmonary resuscitation), no-flow times were relatively low overall. This is because most studies included in-hospital cardiac arrest, witnessed out-of-hospital cardiac arrest with bystander CPR, or low no-flow times mandated within their institutions. (No-flow time is the reported time from cardiac arrest to the start of CPR by a bystander or medical provider.) Generally, survival and neurological outcomes deteriorate as the durations of no-flow and conventional CPR increase before ECPR is deployed.[8]

Cardiogenic Shock

None of the observational studies of patients with cardiogenic shock used propensity score matched analyses. The studies of cardiogenic shock included patients with a wide variety of etiologies (e.g., postinfarction or decompensated cardiomyopathies, postcardiotomy cardiogenic shock) and comparators (percutaneous VAD, LVAD, intra-aortic balloon pump).[8] In addition, Ouweneel et al[8] noted differences in the definition of refractory cardiogenic shock among the studies. Mohite et al[27] suggested the ECMO group had poorer results compared with people who received a temporary VAD because the study centre did not routinely apply an additional cannula as a standard procedure to offload the left atrium and alleviate left ventricular distention. In many of the cardiogenic shock studies, the decision to use ECMO for a particular patient was based on the judgment or discretion of the attending physician and on the availability of ECMO during the patient enrollment dates.

Additional Observations

For both cardiac arrest and cardiogenic shock, very few studies reported the number of patients receiving ECPR or ECMO who were successfully weaned off the machine or bridged to a long-term VAD or heart transplant, compared with those receiving conventional treatment.

In general, complications were poorly reported within the included studies.[8] One study of cardiac arrest reported a greater number of ECPR-treated patients who experienced leg ischemia or malperfusion, compared with patients who received traditional CPR.[38] For cardiogenic shock, two studies reported no significant difference in complications between patients who received ECMO or percutaneous VADs.[42,44] One study reported significantly more septic shock and systemic inflammatory response in patients treated with ECMO compared with VADs.[27] The value of complications in these extremely high-risk patients may be relative as survival with good neurological outcome might outweigh the risk for complications.[8]

The included studies rarely reported the outcomes of time in intensive care or length of stay, limiting conclusions on the impact of ECMO and ECPR on these outcomes.

Conclusions

For adults treated for refractory cardiac arrest:

- Extracorporeal cardiopulmonary resuscitation (ECPR) may improve 30-day survival compared with conventional cardiopulmonary resuscitation (CPR), but we are very uncertain (GRADE: Very Low)
- ECPR may improve long-term survival compared with conventional CPR (GRADE: Low)
- ECPR may improve 30-day favourable neurological outcome compared with conventional CPR, but we are very uncertain (GRADE: Very Low)
- ECPR likely improves long-term favourable neurological outcome compared with conventional CPR (GRADE: Moderate)
- ECPR may be associated with a significant increase in treatment-related complications, such as leg ischemia/malperfusion, bleeding, or hematoma with need for transfusion, compared with conventional CPR (GRADE: Low)

For adults treated for refractory cardiogenic shock:

- Venoarterial extracorporeal membrane oxygenation (ECMO) may not result in a difference in 30-day survival compared with percutaneous ventricular assist devices, but we are very uncertain (GRADE: Very Low)
- ECMO may improve 30-day survival compared with intra-aortic balloon pump, but we are very uncertain (GRADE: Very Low)
- ECMO may be associated with worsened 30-day and long-term survival compared with nonpercutaneous ventricular assist devices, but we are very uncertain (GRADE: Very Low)
- ECMO may be associated with a significant increase in systemic inflammatory response compared with ventricular assist devices in patients with postcardiotomy cardiogenic shock, but we are very uncertain (GRADE: Very Low)

ECONOMIC EVIDENCE

Research Questions

1. What is the cost-effectiveness of venoarterial extracorporeal membrane oxygenation (VA ECMO) for extracorporeal cardiopulmonary resuscitation (ECPR) compared with standard care in adults with refractory cardiac arrest?
2. What is the cost-effectiveness of VA ECMO compared with conventional treatment or other short-term mechanical circulatory supports in adults with refractory cardiogenic shock?

Methods

Economic Literature Search

We performed an economic literature search on September 21, 2018, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until September 21, 2018
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Unpublished studies

Population

1. Adults (≥ 18 years) with refractory cardiac arrest
2. Adults (≥ 18 years) with refractory cardiogenic shock

Interventions

1. VA ECMO for ECPR
2. VA ECMO

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios (ICERs)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[33] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, ICERs)

Study Applicability

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[45] We retained questions from the NICE checklist related to study applicability and modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. We assessed the applicability of each study to the research question (directly, partially, or not applicable).

Results

Literature Search

The economic literature search yielded 448 citations published from database inception until September 21, 2018, after removing duplicates. We identified five economic-related studies that met our inclusion criteria. Figure 7 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

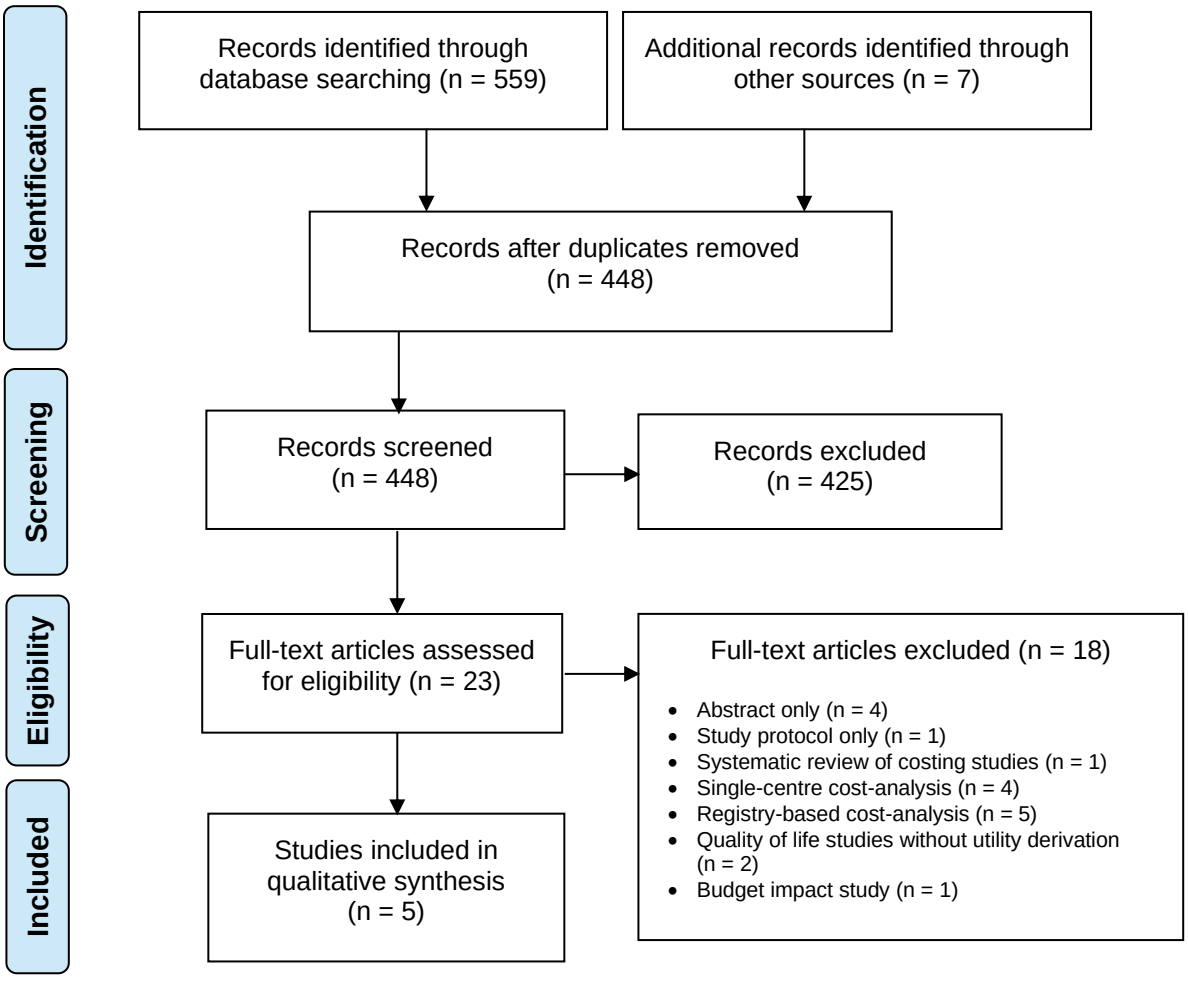

Figure 7: PRISMA Flow Diagram—Economic Search Strategy

Source: Adapted from Moher et al, 2009.[22]

Overview of Included Economic Studies

Table 6 summarizes the results of the five included studies.

Nance and Sistino[46] (United States, 2006) developed a Markov transition model to determine the optimum strategy for using VA ECMO, temporary ventricular assist devices (TVAD), and temporary biventricular assist devices (TBiVAD) for the management of patients with postcardiotomy cardiogenic shock. Their hypothesis was that supporting the patient on ECMO

before instituting TVAD (or TBiVAD) would reduce cost and allocate resources in a more cost-effective manner. The model was used to determine the economically optimal time for initiation of TVAD (or TBiVAD). The total costs associated with support began to level out between days 6 and 10 using an Abiomed BVS5000 ventricular assist device, starting at $47,285 USD per life saved for an initial 1 day on ECMO and decreasing to $26,228 USD per life saved for an initial 6 days on ECMO. The authors concluded that patients should be supported on ECMO for at least 2 to 3 days to evaluate their potential for recovery before instituting more expensive ventricular assist devices. The model's transition probabilities were estimated using a retrospective review of registry records of 17 patients. For support using TVAD (or TBiVAD) for a maximum of 12 days, the authors considered only the device cost, but for ECMO the cost of 24-hour monitoring was also calculated. The small sample size used to inform the model's parameters (only 17 patients), very short period of follow-up, not considering the full costs associated with placement and monitoring of devices, and ignoring the costs of treating complications are major limitations of this study.

Roos et al[47] (Germany, 2013) conducted a cost–utility analysis to compare percutaneous ventricular assist devices (pVAD, specifically Impella 2.5) with either intra-aortic balloon pump (IABP) or VA ECMO for patients who underwent a high-risk percutaneous coronary intervention (PCI). Registry data on the short-term effectiveness and safety of pVAD were combined with various published clinical studies to construct a Markov transition model for each strategy. The study showed that, at 10 years, pVAD generated a total cost of €36,169 for 4.06 quality-adjusted life-years (QALYs), IABP cost €27,792 for 3.84 QALYs, and ECMO cost €23,246 for 2.79 QALYs. ECMO was less costly and less effective compared to either pVAD or IABP. The authors concluded that, compared with either IABP or ECMO, pVAD was a cost-effective intervention for high-risk PCI patients, with respective ICERs of €38,069 and €27,193 per QALY. A major methodological limitation of this study is that the populations in the clinical studies used for parameterizing the model were not similar; the population in the ECMO study was patients with postcardiotomy cardiogenic shock.

Maini et al[48] (United States, 2014) used 2010–2011 U.S. national registry data for patients with acute myocardial infarction complicated by cardiogenic shock and built a Markov transition model to assess cost-effectiveness of percutaneous ventricular assist devices (pVAD, specifically Impella or TandemHeart) in comparison to using central surgical VA ECMO or temporary left ventricular assist devices (LVAD). They also compared these two with an Impella-only strategy guided by their protocol developed at PinnacleHealth (a U.S. health care provider). Empirical data were used to determine the probability of survival during the index hospital admission in the model. The cost of the index hospital admission varied by strategy. The total cost for 3 years of follow-up was calculated at $112,340 USD for pVAD, $158,218 for the surgical strategy (central ECMO or LVAD), and $76,234 for the PinnacleHealth strategy. The corresponding life-years gained (LYG) were 1.32 for pVAD, 0.98 for surgical, and 1.38 for PinnacleHealth. Both pVAD and PinnacleHealth dominated the surgical alternative with higher LYG and lower costs, and PinnacleHealth dominated pVAD with higher LYG and lower costs. The authors concluded that pVAD support offered a less invasive alternative and resulted in better outcomes and lower costs than traditional surgical hemodynamic support alternatives (ECMO or LVAD) that can be deployed sooner. Considering that, in current practice, central surgical ECMO and central surgical LVAD are mostly used for patients who have had or are expected to have open surgery, the comparison of these support strategies with pVAD for cardiogenic shock following acute myocardial infarction, as was done in this study, would not be appropriate for contemporary settings. In addition, the more appropriate comparator, peripheral ECMO (in which the canula are inserted in a femoral artery), can be placed as quickly, if not faster, than Impella or TandemHeart.

St-Onge et al[49] (Canada, 2015) used a decision tree analytic model to evaluate the cost-effectiveness of VA ECMO compared with standard care for adults with severe shock or cardiac arrest secondary to cardiotoxicant poisoning (a serious condition that can be caused by certain cardiovascular drugs). The authors took a lifetime horizon and a societal perspective. Intervention effectiveness and transition probabilities used in the model were taken from a small observational study and were combined with estimates from a systematic review. In a micro-costing approach, estimated expenses for different medical and nonmedical items, including patient transfer, were taken from various sources. The ICER was estimated to be $7,185 CAD per LYG, based on their reference assumption of 100% survival with VA ECMO for patients with cardiac arrest and 83% for patients with severe shock. However, when survival estimates from an alternative registry were used (27% for cardiac arrest and 39% for cardiogenic shock), the ICER increased to $34,311 per LYG. The result of their probabilistic sensitivity analysis showed that effectiveness is only achieved in 51% of the cases. The population for this study could be considered a subset of our target population, but the transient nature of cardiotoxicant poisoning and its specific pathways limit the applicability of the results to a general population of adults with cardiogenic shock or cardiac arrest.

Chang et al[50] (Taiwan, 2017) used a Markov model to compare the cost–utility of two approaches for patients with refractory heart failure and waiting for heart transplantation: a temporary ventricular assist device (TVAD, CentriMag) used as a direct bridge to heart transplantation, compared with double bridges—VA ECMO followed by TVAD. Probabilities and direct cost data were calculated from a nationwide claims database, and utility inputs were adopted from published sources. The direct TVAD strategy had lower lifetime costs (USD $95,910 vs. USD $129,516) but higher lifetime QALYs than the double-bridge strategy (1.73 vs. 0.89). Their probabilistic sensitivity analysis showed the probability that direct TVAD was cost-effective exceeded 75% at any level of willingness-to-pay. The authors concluded direct TVAD bridge to heart transplantation was more cost-effective than the double-bridge strategy in patients with refractory heart failure. There are two limitations to this study. First, the two populations used for model calibration may be different with respect to severity of disease because ECMO might have been initiated more frequently than TVAD in severe and urgent cases. Second, the validity of extrapolating rates of events to the long term (years) is questionable when the device under study (TVAD, CentriMag) was intended for short-term support (1 month or less, a few months in exceptional circumstances).

Table 6: Results of Economic Literature Review—Summary

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Nance and Sistino, 2006,[46] United States	Cost-minimization analysis Markov state-transition model Perspective of hospital 12-day time horizon	Adult patients with postcardiotomy cardiogenic shock	Days on VA ECMO before allowing the switch to TVAD or TBiVAD (BVS5000)	Number of patients survived: NR	2006 USD Discount rate: NA Total costs: NR	Cost per life saved: $47,285 (for 1 initial day on ECMO), minimizing at $26,228 (for 6 initial days on ECMO)
Roos et al, 2013,[47] Germany	Cost–utility analysis Markov state-transition model Perspective of Germany's state health insurance 10-year time horizon	Patients who underwent a high-risk PCI Age: 71.8 years (± 9.9) % male: 81.3	pVAD (Impella 2.5) IABP VA ECMO	QALYs: 4.06 for pVAD, 3.84 for IABP; and 2.79 for ECMO	2011 Euro Discount rate: 3.5% Total cost: €36,169 for pVAD; €27,792 for IABP; and €23,246 for ECMO	ECMO was less costly and less effective compared to either pVAD or IABP ICER (€/QALY): 27,193 for pVAD vs. ECMO; 3,003 for IABP vs. ECMO; and 38,069 for pVAD vs. IABP (69% probability of being cost-effective at €50,000/QALY threshold)
Maini et al, 2014,[48] United States	Cost-effectiveness analysis Markov state-transition model Perspective of U.S. private insurers 3-year time horizon	Patients with AMI complicated by cardiogenic shock Mean age: 69.2 years for pVAD, 63.8 years for surgical alternatives	pVAD (Impella, TandemHeart) Surgical alternatives (central VA ECMO or LVAD) PinnacleHealth's pVAD protocol (Impella 2.5)	LYG: 1.32 for pVAD; 0.98 for surgical; and 1.38 for PinnacleHealth	2014 USD Discount rate: NR Total cost: $112,340 for pVAD; $158,218 for surgical; and $76,234 for PinnacleHealth	Both pVAD and PinnacleHealth dominated surgical alternatives with higher LYG and lower costs PinnacleHealth dominated pVAD with higher LYG and lower cost (robust under sensitivity analysis)

Author, Year, Country of Publication	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention(s) and Comparator(s)	Results		
				Health Outcomes	Costs	Cost-Effectiveness
St-Onge et al, 2015,[49] Canada	Cost-effectiveness analysis Markov state-transition model Perspective of Canadian society at large Lifetime horizon	Adults in shock or in cardiac arrest secondary to cardiotoxicant poisoning	VA ECMO Standard therapy	Life-years gained (LYG): 18 for VA ECMO; and 10 for standard therapy	2013 CAD Discount rate: NR Total cost: $145,931 for ECMO; and $88,450 for standard therapy	ICER ($/LYG): 7,185 for ECMO vs. standard therapy using reference survival assumptions; and 34,311 using pessimistic survival assumptions
Chang et al,[50] 2017, Taiwan	Cost–utility analysis Markov state-transition model Perspective of Taiwan's national health insurance Lifetime horizon	Adults with refractory heart failure	TVAD bridge to heart transplant (CentriMag) Double bridge to heart transplant (VA ECMO followed by TVAD)	QALYs: 1.73 for TVAD bridge; and 0.89 for double bridge	2017 NTD and USD Discount rate: 3% Total cost: NTD 2,973,203 (USD 95,910) for TVAD bridge; and NTD 4,014,991 (USD 129,516) for double bridge	Direct TVAD strategy dominated double-bridge strategy with higher QALYs and lower cost (> 75% probability of being cost-effective at any WTP value)

Abbreviations: AMI, acute myocardial infarction; CAD, Canadian dollars; IABP, intra-aortic balloon pump; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NR, not reported; NTD, Taiwanese new dollars; PCI, percutaneous coronary intervention; pVAD, percutaneous temporary ventricular assist device; QALY, quality-adjusted life-year; TBiVAD, temporary biventricular assist device; LVAD, temporary left ventricular assist device; TVAD, temporary ventricular assist device; USD, U.S. dollars; VA ECMO, venoarterial extracorporeal membrane oxygenation; WTP, willingness-to-pay.

Applicability of the Included Studies

Appendix 7, Table A8, provides the results of the applicability checklist for economic evaluations applied to the included studies. All were deemed partially applicable to the research question. None of the studies were representative of our indications for intended patient populations. However, we benefited from the patient pathways discussed in these studies in building our model for a primary economic evaluation.

Discussion

We conducted an economic evidence review to identify any relevant economic evaluations assessing the cost-effectiveness of VA ECMO for cardiogenic shock and VA ECMO used as extracorporeal cardiopulmonary resuscitation (ECPR) for cardiac arrest, compared with conventional management (i.e., drugs or conventional cardiopulmonary resuscitation) or other temporary mechanical circulatory support devices (i.e., IABP, PTVAD, or TVAD). Our review identified five studies, and all were partially applicable to our research question. Only one study[49] used a Canadian perspective, but its indications (cardiotoxicant-induced shock or cardiac arrest secondary to cardiotoxicant poisoning) were different from the indications considered in this health technology assessment. Of the other four studies, one[50] used a different intervention/comparator pair from ours, and another study[46] aimed to find the optimal time to initiate ECMO for one of our indications of interest (postcardiotomy support). The third study[48] compared percutaneous or temporary surgically implanted VADs with surgical ECMO only, and the fourth study[47] considered high-risk percutaneous coronary interventions, which is different from the intended indications in our health technology assessment.

Conclusions

Existing cost-effectiveness analyses had inconsistent and inadequate results to allow us to make any conclusion about VA ECMO for adults with cardiogenic shock or cardiac arrest. The most notable limitation of almost all studies was the incomparability of the populations for the intervention and the comparator. In the absence of randomized controlled trials, the available registry-based data should be used with caution to ensure a fair comparison of effectiveness and costs.

PRIMARY ECONOMIC EVALUATION

The published economic evaluations identified in the economic literature review addressed only limited aspects of using extracorporeal membrane oxygenation (ECMO) for refractory cardiogenic shock or cardiac arrest, and therefore we could not use them to make conclusions about the cost-effectiveness of ECMO for either indication. Further, only one study[49] took a Canadian perspective, and that was for a minor subgroup of our intended patients (people with cardiotoxicant poisoning). Owing to these limitations, we decided to conduct primary economic evaluations to assess the cost-effectiveness of ECMO for refractory cardiogenic shock and cardiac arrest.

However, our clinical evidence review found the quality of evidence for survival and other outcomes to be very low for ECMO used for refractory cardiogenic shock, and low to very low for refractory cardiac arrest. Specifically, we noticed the following about the evidence:

- Cardiogenic shock studies were methodologically poorer than cardiac arrest studies since none used a propensity score matched analysis, whereas all the cardiac arrest studies in the meta-analysis used propensity matched analyses
- Cardiac arrest studies had fewer “Very Low” GRADE ratings than cardiogenic shock studies
- Cardiac arrest studies used one comparator; in contrast, among the cardiogenic shock studies, two used intra-aortic balloon pump (IABP) as a comparator, two used TandemHeart/Impella as a comparator, and one used left ventricular assist device (LVAD) as a comparator
- 30-day survival significantly improved with ECMO only in the IABP comparator studies; when ECMO was compared to Impella/TandemHeart there was no significant difference, and ECMO did significantly worse with LVAD as the comparator
- All the cardiac arrest studies reported short- and long-term survival and short- and long-term favourable neurological outcomes, while only one cardiogenic shock study reported long-term survival (LVAD comparator) and none reported neurological outcome

Therefore, we did not pursue a primary economic evaluation for the use of ECMO in refractory cardiogenic shock because of the substantial uncertainty and heterogeneity in clinical inputs and paucity of long-term follow-up data.

Research Question

What is the cost-effectiveness of venoarterial extracorporeal membrane oxygenation used as extracorporeal cardiopulmonary resuscitation (ECPR), compared with conventional cardiopulmonary resuscitation (CPR), in adults (≥ 18 years of age) with refractory cardiac arrest, from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[51]

Analysis

We conducted a cost-effectiveness analysis to measure the costs and life-years gained (LYGs) gained of adopting ECPR versus conventional CPR. We chose this approach because the most important health-related outcome considered here, survival, is measured using life-years gained. We also measured and reported the number of organ donations, as a secondary outcome. We were unable to find quantitative utility studies suitable for the health states involved in the care pathways for the intervention and comparator and hence did not perform a cost–utility analysis.

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis adhered to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines[52] when appropriate and represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

The secondary health economist conducted a formal internal validation. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.[52]

Target Population

Our target population was adults (age ≥ 18 years) eligible for ECPR after presenting with cardiac arrest refractory to conventional cardiopulmonary resuscitation.

We ran separate analyses for populations with in-hospital cardiac arrest (mean age 63.2 years) and out-of-hospital cardiac arrest (mean age 52.6 years) because the reported effectiveness outcomes showed significant differences between the two groups.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Intervention

We conducted evaluations for ECPR compared with conventional CPR. Table 7 summarizes the interventions evaluated in the economic model.

Table 7: Disease Intervention and Comparator Evaluated in the Primary Economic Model

Intervention	Comparator	Patient Population	Outcomes
ECPR	Conventional CPR	Adults with refractory cardiac arrest	Cost, LYG, organ donations, ICER

Abbreviations: CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ICER, incremental cost-effectiveness ratio; LYG, life-years gained.

Discounting and Time Horizon

To fully capture the comparative effects of survival and neurologically intact survival, we used a lifelong time horizon in our analyses. In scenario analyses, we used shorter time horizons. In accordance with the CADTH guidelines, we applied an annual discount rate of 1.5% to both costs and life-years incurred after the first year.

Main Assumptions

The main assumptions for our model were as follows:

- We only considered a one-time use of ECPR, which means we did not model possible future episodes of cardiac arrest in the same individual
- Only one device was applied at each intervention. This means we did not model the practice of starting with one mechanical support, for example IABP, and then changing to ECPR. Also, we did not model hybrid configurations such as ECPR combined with a non-ECMO temporary mechanical support (used for improved venting/unloading)
- We did not find sufficient clinical evidence to inform the potential benefits for destination therapies (long-term ventricular assist device or heart transplant) after ECPR, and hence did not model those pathways
- Although it is possible that a patient's neurological state changes after discharge, either worsening or improving, we did not find quantitative evidence for such changes (in the literature or reported registries), and hence did not model these potential movements in our analysis
- We did not find any evidence for additional costs directly attributable to ECPR or the comparator after hospital discharge. However, most people who survive a cardiac arrest will need some sort of cardiovascular monitoring or preventive treatment immediately and possibly for many years. Therefore, for neurologically favourable survivors of cardiac arrest, we used an average yearly cost for medication taken from post-discharge studies of patients with myocardial infarction, assuming post-discharge medications were similar between the ECPR and comparator groups. For neurologically poor survivors, we used the average daily cost of long-term care homes in Ontario
- In cardiac arrests, the patient population is heterogeneous, and so the treatment offered to address the underlying cause could vary. However, we assumed the course of the treatment was similar, on average, for the intervention and comparator groups in our model. Therefore, we only considered the costs directly related to the use of ECPR or conventional CPR. This approach extended to long-term follow-up of survivors, where we only considered costs of the most common medications
- We did not find any credible comparative evidence of differences in length of stay in an intensive care unit (ICU) for people receiving ECPR versus conventional CPR. Therefore, we set a minimal duration for ICU stay, equivalent to the duration of ECPR

Model Structure

We developed a Markov model (Figure 8) for cardiac arrest to determine the incremental cost per life-year gained for the intervention (ECPR) versus usual care (conventional CPR). We used monthly cycles for the first year (12 cycles) and yearly cycles afterwards.

In the model, a patient cohort is assigned to either intervention (ECPR) or usual care (conventional CPR) (Figure 8). The initial states are "ECPR initiation and maintenance" for the intervention pathway and "continue conventional CPR" for the usual care pathway. Patients stay for the first cycle in this state, and those in the ECPR pathway are at risk of complications associated with the procedure (i.e., mechanical failure, bleeding, infection, limb ischemia or amputation). At this stage,

for both groups, the goal is to return the patient to a stable hemodynamic condition. If the patient regains natural cardiac function, they move to one of two "post–CA care" states, representing the possibility of either favourable or poor neurological outcomes after recovery from cardiac arrest (see clinical evidence review for details).

If the treatment is unsuccessful, the patient is assessed for the potential to be an organ donor. Those eligible move to a substate within the "dead" health state that accounts for organ donations. Patients moving to this state are (or expected to be) declared clinically dead but are kept on ECPR to preserve organ function. We did not model life-years gained for potential recipients of these organs or the costs involved in the organ donation process. Patients for whom treatment is declared futile, and organ donation is not considered or refused, go through palliative withdrawal of ECPR. We did not consider any costs associated with moving to the "dead" state.

In our model, the states and the structure of the transitions are the same for the intervention and comparator, but the probability of transitions and the associated costs in each state are unique to each group.

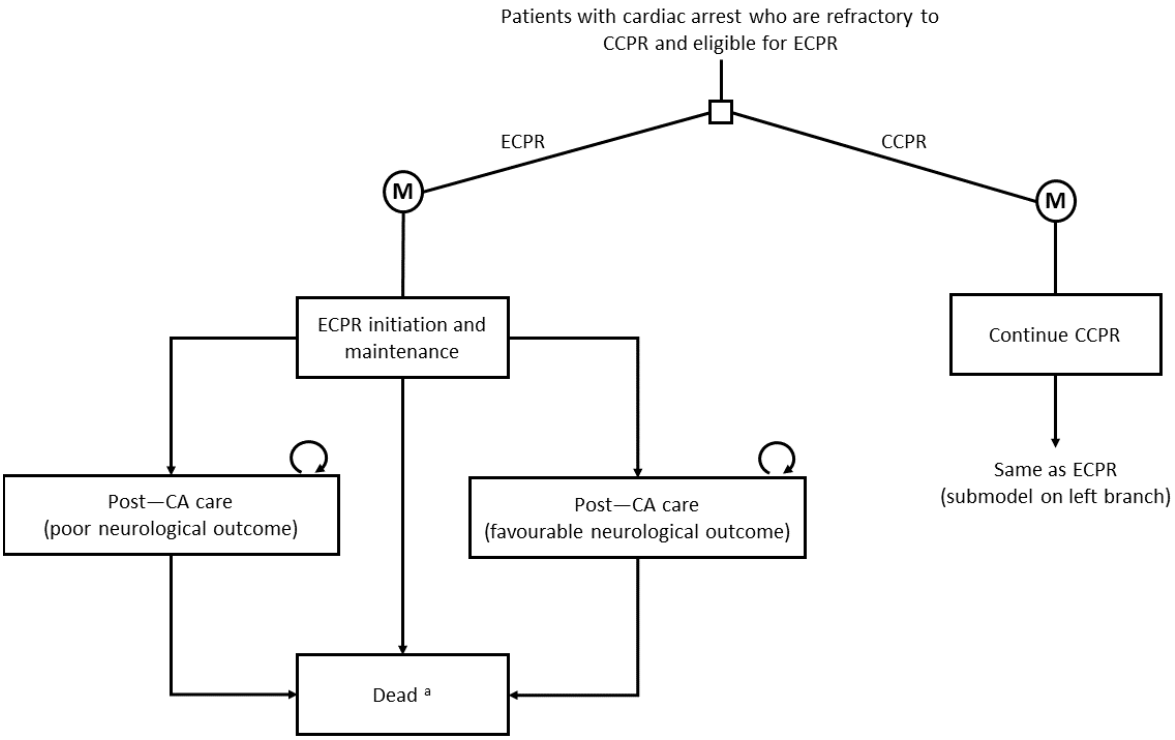

Figure 8: Markov Model for the Treatment of Adults With Cardiac Arrest

Abbreviations: CA, cardiac arrest; CCPR, conventional cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation.
[a]Some individuals who do not survive the initial treatment would be eligible to be organ donors.

Clinical Outcomes and Parameters

We used several input parameters to populate the model:

- Variables used to model the natural history of cardiac arrest
- Variables used to modify the natural history model to account for treatment effects of ECPR
- Variables used to capture survival (i.e., life-years)

Natural History of Cardiac Arrest

If untreated, cardiac arrest will, in most cases, result in death or severe irreversible organ damage (especially brain damage). The conventional treatments (e.g., drugs, conventional CPR) work for a subset of patients to return them to a state of adequate hemodynamic support. In our model, we used rates for major outcomes with conventional treatment (Table 8) estimated from the published clinical literature. Overall, the rate of survival following cardiac arrest is low, given the condition's severity, but there is evidence of significant improvements in survival with ECPR versus conventional CPR.

Impact of Extracorporeal Cardiopulmonary Resuscitation on the Natural History of Cardiac Arrest

Table 8 lists the relative rates of key outcomes (survival, poor or favourable neurological outcome, and successful organ donation), showing potential improvement from using ECPR versus conventional CPR. Table 9 lists the rates of complications associated with ECPR (e.g., bleeding and infection). We estimated these values from the clinical literature. In our model, complications occur only in the initial state ("ECPR initiation and maintenance"), where they are applied one time according to their probability and only affect the cost. The survival-related parameters are the same as those discussed in the clinical section of this report, except that we calculated conditional survival probabilities for after discharge (intervention specific) and conditional long-term mortality probabilities (independent of intervention choice). We derived the conditional probabilities by taking the difference between reported numbers for short- and long-term survival and neurologically favourable survival and either meta-analyzing or pooling the study results. For organ donation, we performed a nonsystematic search to identify relevant literature and calculated pooled intervention-specific estimates. For the complications specific to ECPR, we used the values reported in the registry data of the Extracorporeal Life Support Organization.[53]

To model post-discharge survival, we divided it into three subperiods: up to 3 months or 1 year after discharge, a longer period after the initial follow-up (up to 6 years), and a final period lasting until death or the end of our analysis horizon. The survival rate for the first period was taken from ECPR follow-up literature, while in the second period we used the literature for cardiac arrest follow-up, assuming that the type of CPR received would not affect longer-term outcomes. For the final period we used general mortality estimates.

Table 8: Summary Estimates Associated With Conventional and Extracorporeal Cardiopulmonary Resuscitation

Model Parameters	CCPR, Probability (CI)	ECPR vs. CCPR, Relative Risk (CI)	Reference
Probability of survival to discharge following cardiac arrest			
In-hospital cardiac arrest	0.15 (0.10, 0.22)	2.07 (1.25, 3.43)	Meta-analysis[30,36,38]
Out-of-hospital cardiac arrest	0.17 (0.13, 0.21)	1.18 (0.71, 1.97)	Meta-analysis[28,32,34]
Probability of neurologically favourable outcome for survivors			
In-hospital cardiac arrest	0.83 (0.61, 0.94)	0.92 (0.71, 1.19)	Meta-analysis[30,36,38]
Out-of-hospital cardiac arrest	0.33 (0.14, 0.60)	1.76 (0.83, 3.73)	Meta-analysis[28,32,34]
Probability of survival following neurologically favourable discharge			
In-hospital cardiac arrest (at 1 year)	0.66 (0.42, 0.84)	1.22 (0.87, 1.70)	Meta-analysis[30,36,38]
Out-of-hospital cardiac arrest (at 3 months)	0.80 (0.30, 0.97)	0.92 (0.34, 2.51)	Meta-analysis[32,34]
Probability of survival following neurologically poor discharge			
In-hospital cardiac arrest (1 year)	0.78 (0.37, 0.96)	0.65 (0.37, 1.13)	Meta-analysis[30,36,38]
Out-of-hospital cardiac arrest (3 months)	0.29 (0.11, 0.59)	1.80 (0.34, 9.38)	Meta-analysis[32,34]
Probability of successful organ donation after nonrecovery, absolute risk (CI)			
In-hospital cardiac arrest	0.013 (0.011, 0.015)	0.151 (0.069, 0.298)	Pooling[54-56]
Out-of-hospital cardiac arrest	0.068 (0.034, 0.129)	0.344 (0.226, 0.485)	Pooling[57-67]
Risk of death following cardiac arrest after discharge, up to year 6 after treatment			
In-hospital cardiac arrest (each year after 1st year), mean (SE)		0.1244 (0.0018)	Pooling[68-70]
Out-of-hospital cardiac arrest (each year after 3 months), mean (SE)		0.0284 (0.0027)	Pooling[71,72]
Duration of ECPR, days (CI)	NA	4.39 (4.06, 4.73)	ELSO,[53] 2014–2016
Cohort age, years			
In-hospital cardiac arrest, mean (SE)		63.23 (8.62)	Pooling[30,36,38]
Out-of-hospital cardiac arrest, mean (SE)		52.63 (9.37)	Pooling[28,32,34]

Abbreviations: CCPR, conventional cardiopulmonary resuscitation; CI, confidence interval; ECPR, extracorporeal cardiopulmonary resuscitation; ELSO, Extracorporeal Life Support Organization; NA, not applicable; SE, standard error.

Table 9: Risk of Complications With Extracorporeal Cardiovascular Resuscitation

Complication	Risk Probability, Mean (SE)	Reference
Mechanical failure (oxygenator/pump)	0.076 (0.004)	ELSO[53]; averages calculated using data from 1992–2016
Bleeding at site (surgical/cannulation)	0.167 (0.006)	
Culture-proven infection	0.114 (0.005)	
Limb ischemia	0.041 (0.003)	
Limb amputation	0.004 (0.001)	

Abbreviations: ELSO, Extracorporeal Life Support Organization; SE, standard error.

Cost Parameters

To estimate costs, we searched the clinical literature for procedures and treatments that would be conducted and paid for by the Ontario health system. We cross-referenced results with costs reported in the economic literature to finalize costs specific to Ontario.

We divided the costs into two categories:

- Costs associated with treatment in hospital, including device/equipment costs, hospital operating costs (ICU stay), specialist fees, and costs of treating complications. These costs are relevant for the initial states, “ECPR initiation and maintenance” and “continue CCPR”
- Costs of care for survivors after hospital discharge who recovered with either favourable or poor neurological outcomes. These costs are relevant for the two “post CA-recovery care” survival states

Table 10 itemizes both categories of costs and the sources for our base values and their associated ranges. There are currently three options for ECMO equipment in Canada, with differing capital costs and specific consumables (e.g., cannulas). The costs for these options were informed by consultation with Ontario hospitals (London Health Sciences Centre and University of Ottawa Heart Institute, email communication, January 2019). We distributed these capital costs among the patients and calculated a value using the average yearly number of patients treated and the reported durability of equipment. In scenario and sensitivity analyses, we changed some of these values and explored the impact on the results. The durability, rate of complications, and survival rates might depend on the choice of equipment, but we did not consider such variations because we could not find any definitive evidence.

The inpatient personnel cost includes the costs for a surgeon to place the patient on the ECMO machine, 24-hour monitoring by a perfusionist, and daily visits by a specialist while the patient is on ECMO. We also estimated the costs of treating complications, using various sources. Finally, the costs of long-term treatment after discharge for people with favourable neurological outcomes (daily medication) and with poor neurological outcomes (stay in long-term care) were extracted from relevant Ontario or Canadian sources (Table 10).

Table 10: Costs Used in the Economic Model

Variable	Unit Cost, $	Duration/Quantity	Total Cost Per Patient, $	Reference
Costs associated with hospital treatment				
ECPR equipment (consumables)				
Option 1[a]			4,250	Provided by Ontario hospitals[b]
Option 2			8,950	
Option 3			5,000	
ECPR equipment (reusable capitals)				
Option 1[a]	30,000	Assuming 10% annual service fee, 7 years of capital equipment duration, and 5% annual interest rate, 5 devices per centre, and annual 20 patients per centre[c]	2,046	Provided by Ontario hospitals[b]
Option 2	72,600		4,951	
Option 3	100,000		6,820	
ICU daily stay	3,592			CIHI[73]
Personnel (implantation): Surgeon + anesthesiologist	456.56			MOH[13]
Treatment of complications				
Mechanical failure (oxygenator/pump)		Consumables replaced		
Bleeding of (surgical/cannulation) site	1,414	Blood transfusion		OCCI[74]
Culture-proven infection	1,267	Course of antibiotics		St-Onge et al[49]
Limb ischemia	800	Extra cannula used		
Limb amputation	25,731	Hospital and personnel		St-Onge et al[49]
Personnel (monitoring and maintenance)				
Perfusionist (24-hour monitoring, per hour)	43.97	× 1.5 after 12 hours[d]		McGill HTA[25]
Intensivist (per daily visit):				MOH[13]
Day 1	325.40			
Days 2–30	213.50			
Days 30+	85.35			
Costs of care after hospital discharge				
Ongoing care for people with favourable neurological outcome, average yearly				Dhalla et al[75]
Medication, year 1	2,304.75	Publicly funded for those under age 25 or 65+ years		
Medication, year 2+	1,284.44			
Long-term care for people with poor neurological outcome, average per day	175.75	Long-term care home		Ontario budget, 2018[76]

Abbreviations: CIHI, Canadian Institute for Health Information; ECPR, extracorporeal cardiopulmonary resuscitation; HTA, health technology assessment; ICU, intensive care unit; MOH, Ministry of Health; OCCI, Ontario Case Costing Initiative.

[a]This is the option used in our reference case analysis.

[b]London Health Sciences Centre and University of Ottawa Heart Institute, email communication, January 2019.

[c]Total capital cost per case $= \frac{\text{Equivalent Annual Capital Cost + Annual Service Fee}}{\text{Number of Patients per Year per Centre}}$, where $\text{Equivalent Annual Capital Cost} = \frac{\text{Capital Cost}}{\frac{1-\left(\frac{1}{1+r}\right)^{t}}{r}}$, and where t is the service life (duration) in years and r is the annual interest rate.

[d]Each day is 12 regular hours followed by 12 overtime hours.

Analysis

We calculated the reference case of this analysis by running 10,000 simulations (probabilistic analysis) that simultaneously captured the uncertainty in all parameters that were expected to vary. We set distributions for parameters within the model (Table 11). We calculated mean costs and mean life-years (LY) for each intervention assessed. We also calculated the mean incremental costs, incremental life years gained, and incremental cost-effectiveness ratios (ICERs) as cost per life-year gained for ECPR versus conventional CPR.

We assessed variability and uncertainty in the model using one-way and probabilistic sensitivity analyses. We conducted one-way sensitivity analyses by varying specific model parameters (device/equipment cost, survival/recovery rates, and complication rates) within clinically plausible ranges and examining the impact on the results. Results of the one-way sensitivity analyses are presented in a tornado diagram. The results of the probabilistic sensitivity analysis are presented on a cost-effectiveness plane and a cost-effectiveness acceptability curve.
Table 11 presents the parameters and their corresponding ranges and distributions. For the parameters that have assigned distributions, we used their distributions for probabilistic sensitivity analysis, and the given ranges (95% CI of the distributions or minimum to maximum) for one-way sensitivity analysis. For all other parameters, we used the ranges for one-way sensitivity analysis.

Table 11: Parameters Varied in One-Way and Probabilistic Sensitivity Analyses

Variable	Range	Distribution	Reference
Survival parameters: CCPR	95% CI	Beta	Table 8
ECPR vs. CCPR	95% CI	LogNormal	
Risk of complications: ECPR	95% CI	Beta	Table 9
Cost of ECPR equipment	Base value ± 20%		Table 10
Cost to treat complications	Base value ± 20%		Table 10
Cost of long-term care	Base value ± 50%		Table 10
Duration of ECPR, days	2–20	LogNormal	Table 8
Cohort age, years	18–80	PERT[a]	Table 8

Abbreviations: CCPR, conventional cardiopulmonary resuscitation; CI, confidence interval; ECPR, extracorporeal cardiopulmonary resuscitation.
[a]PERT (also known as Beta-PERT) distribution allows us to parameterize a generalized beta distribution based on expert opinion regarding a pessimistic estimate (minimum value), a most likely estimate (mode), and an optimistic estimate (maximum value).

Results

Reference Case Analysis

Cost-Effectiveness

Table 12 presents the reference case results for our analysis for in-hospital and out-of-hospital cardiac arrest (mean values and 95% credible interval). In both cases, ECPR provided greater life-year gains than conventional CPR, for an incremental cost.

Table 12: Reference Case Analysis Results

Strategy	Average Total Costs, $	Incremental Cost,[a] $	Average Total Effects, LYG[b]	Incremental Effect, LYG[c]	ICER, $/LYG
In-hospital cardiac arrest					
CCPR	33,649 (20,840 to 57,869)[d]		1.3492 (0.7316 to 2.2781)[d]		
ECPR	64,280 (32,860 to 128,519)[d]	30,631 (2,748 to 83,729)[d]	2.9853 (1.2354 to 6.0842)[d]	1.6361 (0.2673 to 4.1964)[d]	18,722
Out-of-hospital cardiac arrest					
CCPR	66,184 (30,601 to 126,113)[d]		1.8221 (0.8524 to 3.1918)[d]		
ECPR	101,097 (31,154 to 293,495)[d]	34,914 (−49,291 to 205,516)[d]	3.0347 (0.8754 to 6.6895)[d]	1.2126 (−0.7845 to 4.4561)[d]	28,792

Abbreviations: CCPR, conventional cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ICER, incremental cost-effectiveness ratio; LYG, life-year gained.
Note: Results might appear incorrect because of rounding.
[a]Incremental cost = average cost of ECPR – average cost of CCPR.
[b]The values reported are discounted. The undiscounted LYs are 1.5846 (CCPR) and 3.5302 (ECPR) with gain of 1.9457 LYs for in-hospital cardiac arrest, and are 2.3123 (CCPR) and 3.9144 (ECPR) with gain of 1.6021 LYs for out-of-hospital cardiac arrest.
[c]Incremental effect = average effect of ECPR – average effect of CCPR.
[d]95% credible interval.

Organ Donation

As a secondary outcome, we present in Table 13 the expected number of successful organ donors after unsuccessful resuscitation from cardiac arrest. ECPR increases the number of donors after both in-hospital and out-of-hospital cardiac arrest.

Table 13: Organ Donation Results

Strategy	Average Number of Donors per 100 People Treated	Incremental Number of Donors[a] per 100 People Treated	Relative Change in Number of Donors[b]
In-hospital cardiac arrest			
CCPR	1.10		
ECPR	10.23	9.13	9.27
Out-of-hospital cardiac arrest			
CCPR	5.61		
ECPR	27.28	21.67	4.86

Abbreviations: CCPR, conventional cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation.
Note: Results might appear incorrect because of rounding.
[a]Incremental number of donners = average number of donors with ECPR – average number of donors with CCPR.
[b]Relative change of number of donors = average number of donors with ECPR ÷ average number of donors with CCPR.

Sensitivity Analyses

One-Way Sensitivity Analysis

Figures 9 and 10 show the tornado diagrams for in-hospital and out-of-hospital cases. For in-hospital cardiac arrest, the most influential parameter is the relative advantage of ECPR over conventional CPR for the probability of neurologically favourable outcome following survival to discharge. The ICER varied (in reverse direction) between $890 per LYG and $36,37 per LYG when we varied this parameter. For out-of-hospital cardiac arrest, the most influential parameter is the probability of survival after neurologically favourable discharge. The ICER varied (in reverse direction) between $21,884 per LYG and $127,392 per LYG when we varied this parameter. For some values of survival parameters, the ICER is negative and ECPR is cost-saving. Other influential parameters (for both in- and out-of-hospital cases) are survival-related probabilities, the cost of long-term care for neurologically poor survivors, and initial age. The ICER for in-hospital cardiac arrest shows fewer changes compared to out-of-hospital cardiac arrest.

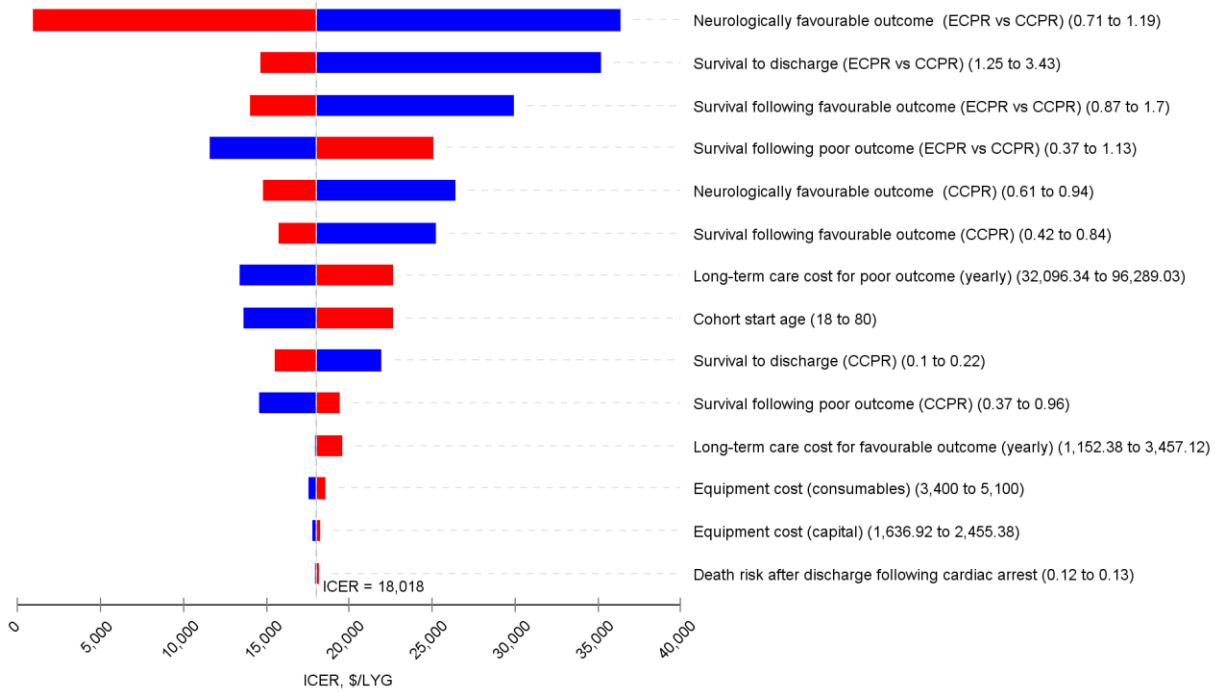

Figure 9: Tornado Diagram for Cost-Effectiveness of Extracorporeal Versus Conventional Cardiopulmonary Resuscitation for In-Hospital Cardiac Arrest

Abbreviations: CCPR, conventional cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ICER, incremental cost-effectiveness ratio; LYG, life-year gained.
Note: For each varying parameter, the red bar represents the result when the higher valued parameter is used, while the blue bar represents the result when the lower valued parameter is used.

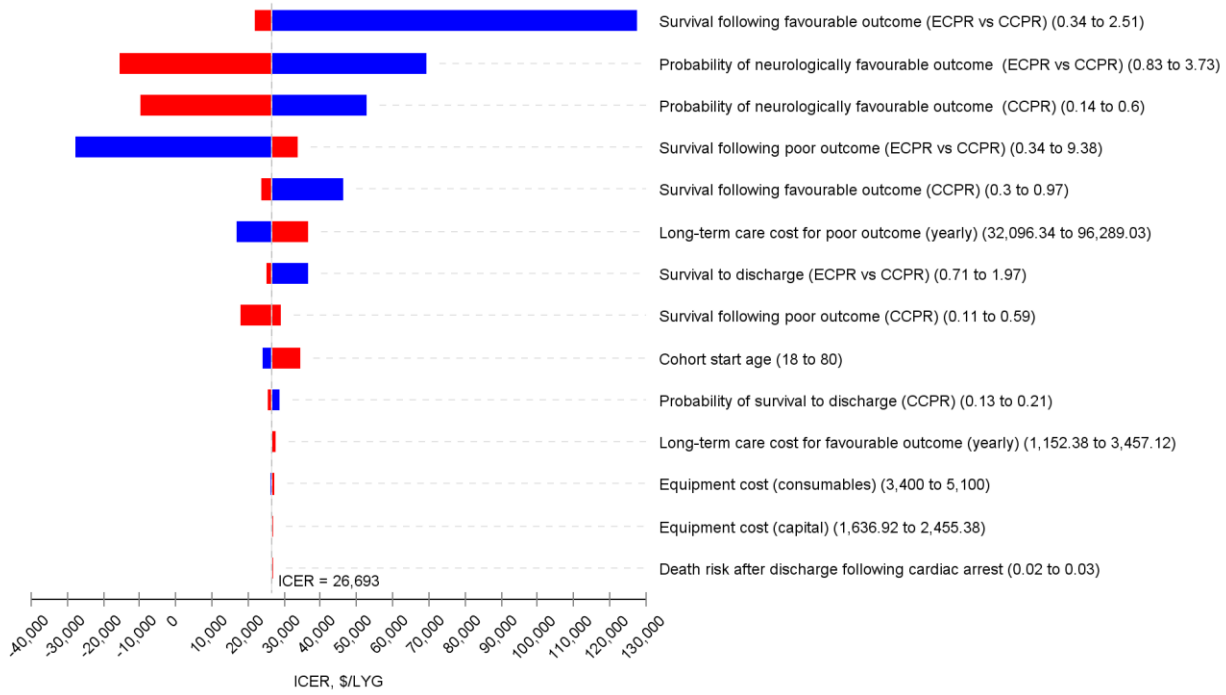

Figure 10: Tornado Diagram for Cost-Effectiveness of Extracorporeal Versus Conventional Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest

Abbreviations: CCPR, conventional cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; ICER, incremental cost-effectiveness ratio; LYG, life-year gained.
Note: For each varying parameter, the red bar represents the result when the higher valued parameter is used, while the blue bar represents the result when the lower valued parameter is used.

Probabilistic Sensitivity Analysis

Figures 11 and 12 show the incremental cost-effectiveness planes, where each point represents one ICER from one Monte Carlo simulation. We ran 10,000 simulations for each case.

In-Hospital Cardiac Arrest

The probability of being in each quadrant indicates that almost all simulations (98.16%) resulted in a positive incremental cost for a positive incremental survival (LYG). Of the remaining simulations, 1.4% were superior (less costly and more effective), 0.39% were inferior (more costly and less effective), and 0.05% were unattractive (less costly and less effective).

Out-of-Hospital Cardiac Arrest

The probability of being in each quadrant indicates that most simulations (62.23%) resulted in a positive incremental cost for a positive incremental survival (LYG). Of the remaining simulations, 21.24% were superior (less costly and more effective), 5.5% were inferior (more costly and less effective), and 11.03% were unattractive (less costly and less effective).

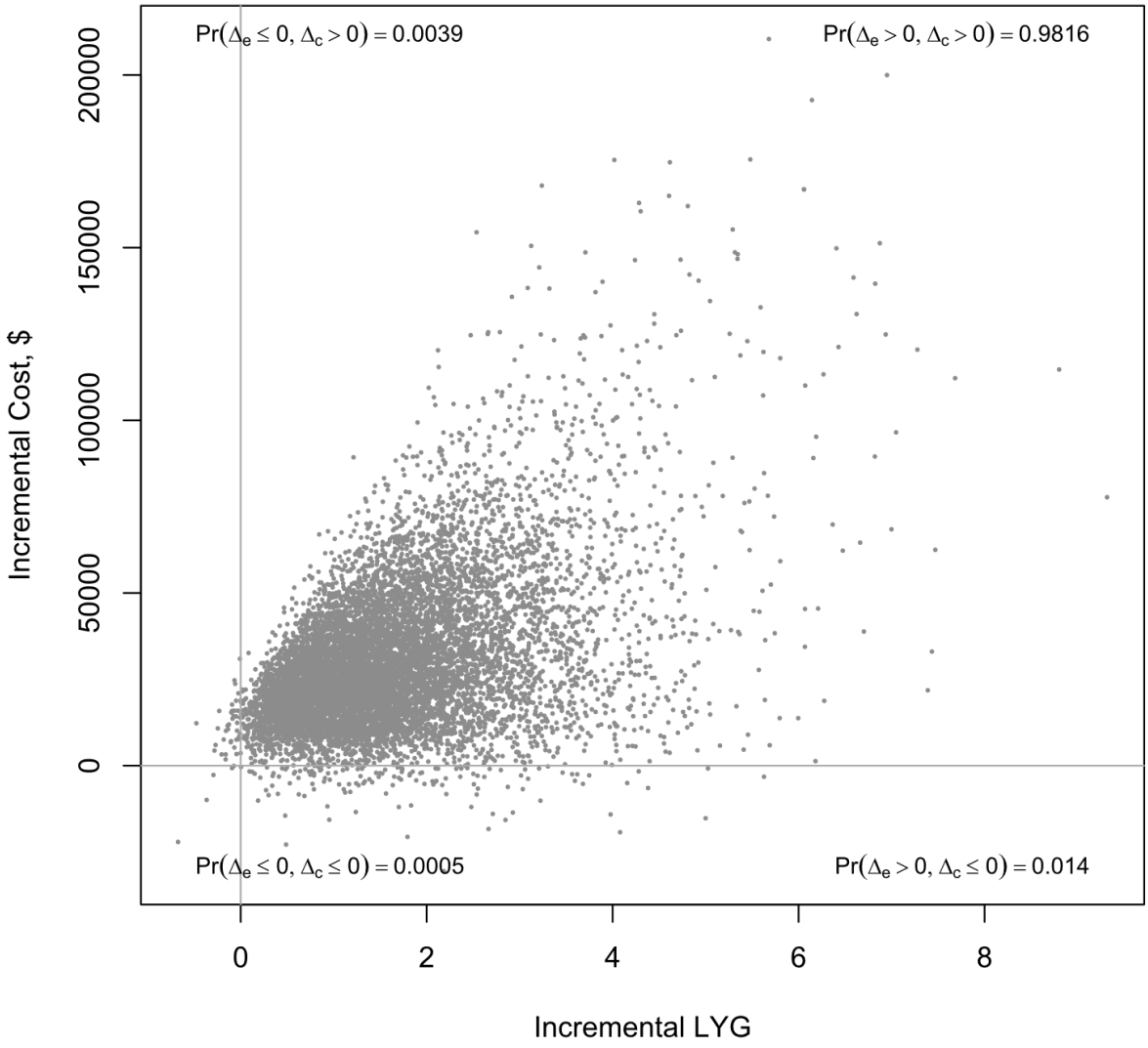

Figure 11: Incremental Cost-Effectiveness Plane for Extracorporeal Versus Conventional Cardiopulmonary Resuscitation for In-Hospital Cardiac Arrest

Abbreviations: Δ_e, incremental effect; Δ_c, incremental cost; LYG, life-year gained; Pr, probability.

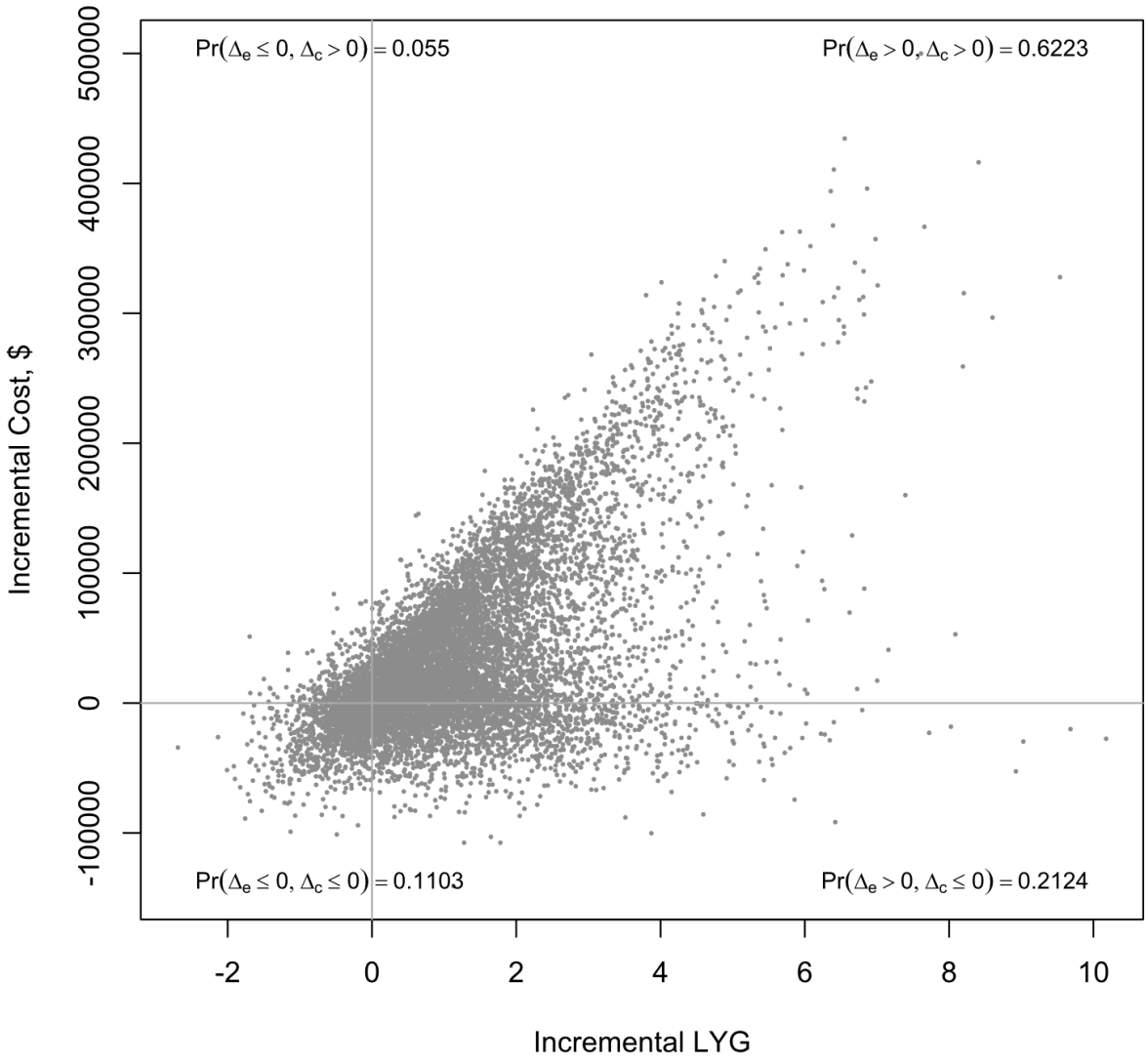

Figure 12: Incremental Cost-Effectiveness Plane for Extracorporeal Versus Conventional Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest

Abbreviations: Δ_e, incremental effect; Δ_c, incremental cost; LYG, life-year gained; Pr, probability.

Figures 13 and 14 show cost-effectiveness acceptability curves for ECPR versus conventional CPR for in-hospital and out-of-hospital cardiac arrest. These curves visually represent the probability of being cost-effective over a range of willingness-to-pay values, up to $100,000 per LYG. For example, for a willingness-to-pay of $50,000 per LYG, the probability of being cost-effective is 0.93 for in-hospital cardiac arrest and 0.60 for out-of-hospital cardiac arrest. They also show that for in-hospital cardiac arrest, after passing the willingness-to-pay value of approximately $20,400 per LYG, ECPR becomes cost-effective in more than 50% of cases. For out-of-hospital cardiac arrest, the approximate similar threshold is $31,000 per LYG.

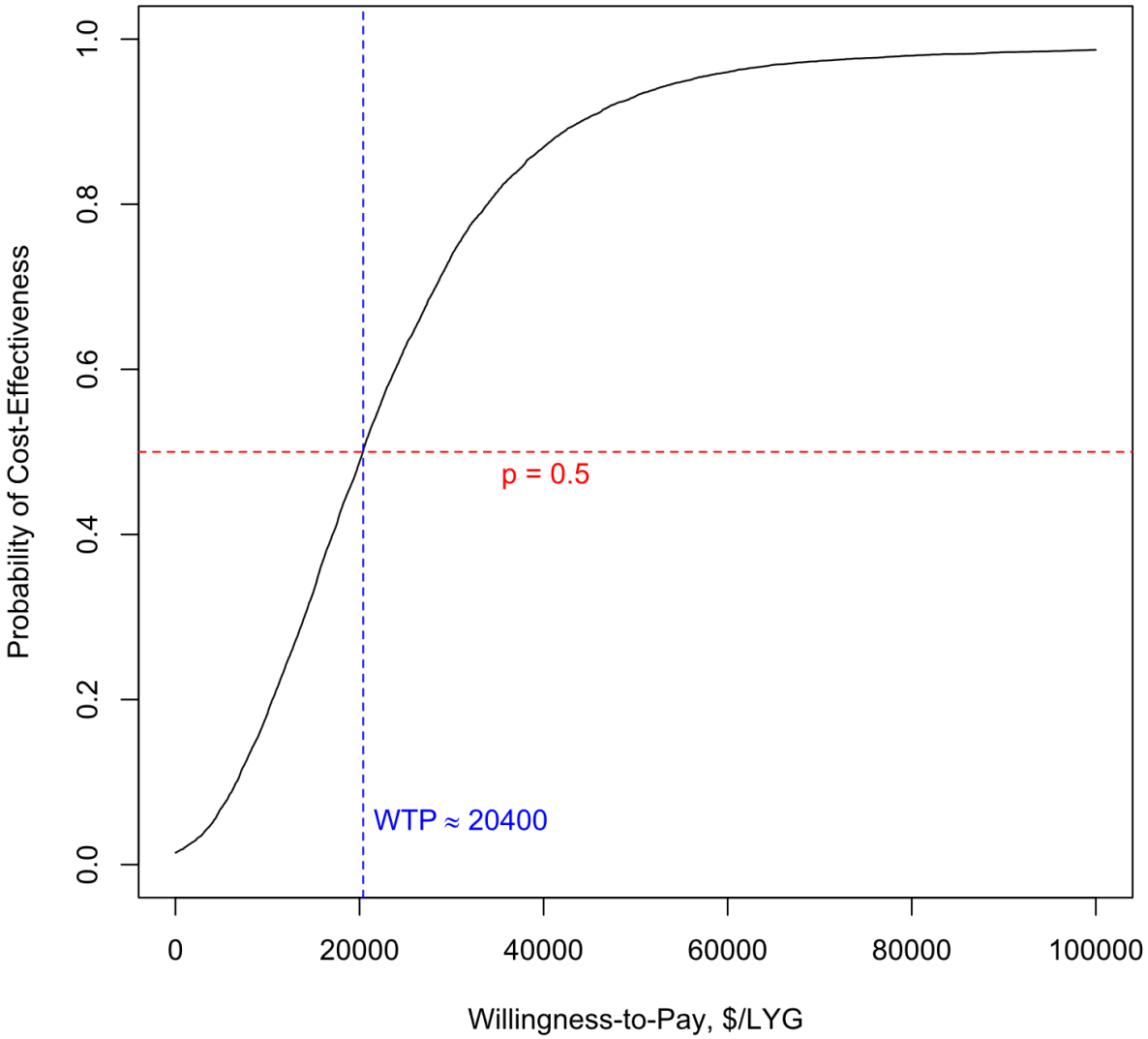

Figure 13: Cost-Effectiveness Acceptability Curve for Extracorporeal Versus Conventional Cardiopulmonary Resuscitation for In-Hospital Cardiac Arrest

Abbreviations: LYG, life-year gained; WTP, willingness-to-pay.

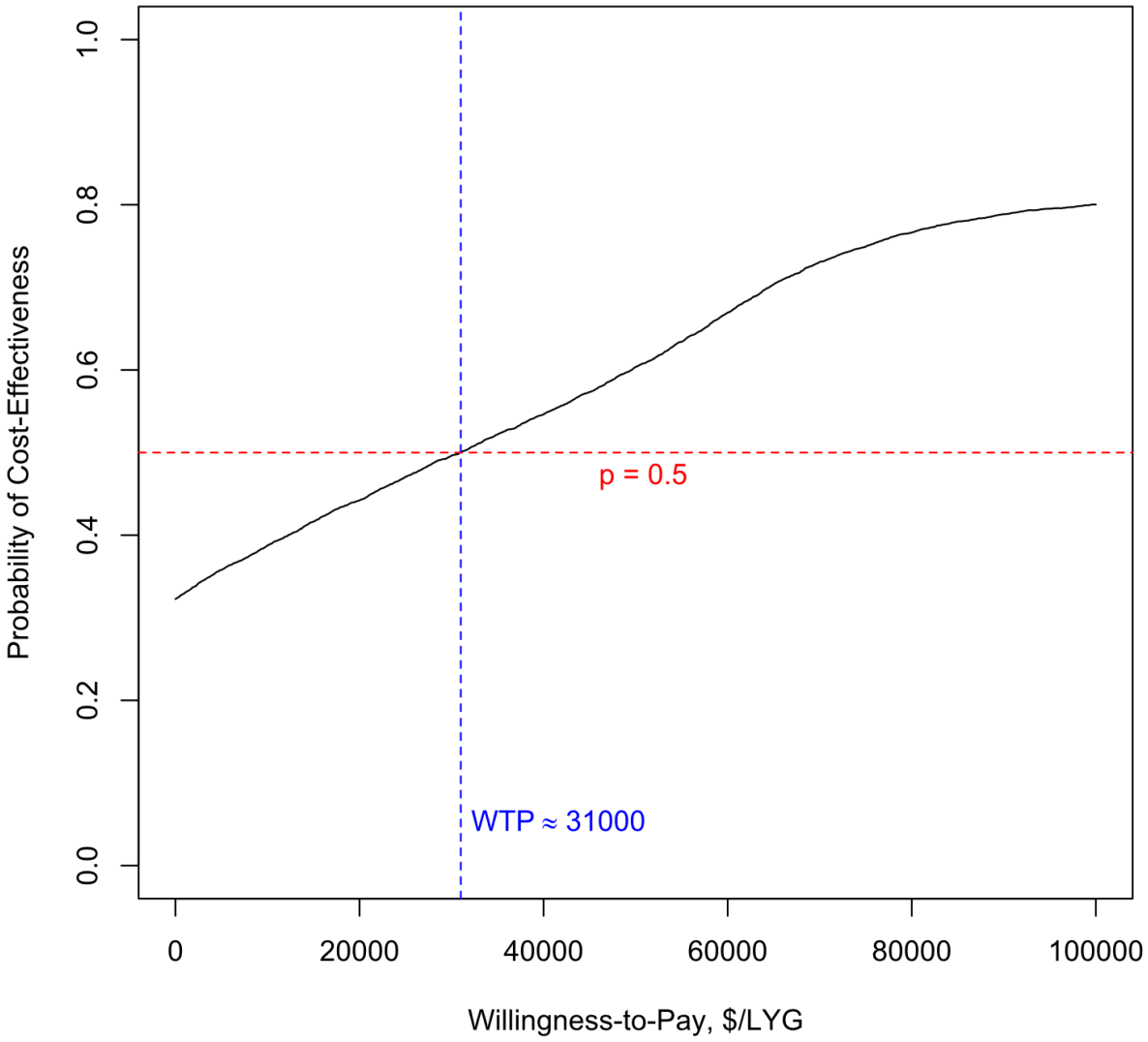

Figure 14: Cost-Effectiveness Acceptability Curve for Extracorporeal Versus Conventional Cardiopulmonary Resuscitation for Out-of-Hospital Cardiac Arrest

Abbreviations: LYG, life-year gained; WTP, willingness-to-pay.

Scenario Analysis

Results show predictable variations under different scenarios. Table 14 presents results for scenarios using a shorter time horizon of 5 years and alternative (most expensive) ECPR equipment (option 3 in Table 10).

For both in-hospital and out-of-hospital cardiac arrest, the ICER increased substantially when a 5-year, rather than lifetime, time horizon was chosen: $35,053 per LYG versus $18,722 per LYG for in-hospital cardiac arrest, and $69,859 per LYG versus $28,792 per LYG for out-of-hospital cardiac arrest.

When we populated the model with data for the most expensive ECPR equipment, the ICER increased only slightly, to $22,383 per LYG for in-hospital cardiac arrest and $32,469 per LYG for out-of-hospital cardiac arrest.

Table 14: Scenario Analysis Results—Shorter Follow-Up Time and Most Expensive Equipment

Scenario	Average Total Costs, $	Incremental Cost,[a] $	Average Total Effects, LYG	Incremental Effect,[b] LYG	ICER, $/LYG
In-hospital cardiac arrest (reference case ICER = $18,722/LYG)					
5-year time horizon					
CCPR	22,526		0.5241		
ECPR	42,029	19,504	1.0805	0.5564	35,053
Most expensive ECPR equipment					
CCPR	33,450		1.3381		
ECPR	69,818	36,368	2.9629	1.6248	22,383
Out-of-hospital cardiac arrest (reference case ICER = $28,792/LYG)					
5-year time horizon					
CCPR	27,156		0.4406		
ECPR	44,260	17,104	0.6855	0.2448	69,859
Most expensive ECPR equipment					
CCPR	66,302		1.8202		
ECPR	106,160	39,858	3.0478	1.2276	32,469

Abbreviations: CCPR, conventional cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation. ICER, incremental cost-effectiveness ratio; LYG, life-year gained;
Note: Results might appear incorrect because of rounding.
[a]Incremental cost = average cost of ECPR – average cost of CCPR.
[b]Incremental effect = average effect of ECPR – average effect of CCPR.

Discussion

We did not conduct a primary economic evaluation for the use of ECMO for patients with cardiogenic shock because there is not sufficient quantitative comparative evidence. This does not mean that ECMO does not have an incremental effect over the standard of care, but simply that any analysis, if attempted, would have very high uncertainty.

Our primary economic analysis was informed by a combination of sources. We took survival probabilities from propensity score matched studies. The rates of complications were taken from a

large international registry. For costs, we used Ontario-specific data for most parameters, including equipment costs, hospital costs, fees for surgeons and other personnel, and costs associated with treatment of complications. We also derived estimated costs for long-term medication and long-term care from Ontario-related studies and documents.

We performed various sensitivity and scenario analyses to test the robustness of our results, changing parameter values and assumptions. Our ICERs for use of ECPR for in-hospital cardiac arrest did not show much unfavourable variation, but for out-of-hospital cardiac arrest, the ICERS varied substantially in some cases. This was because of the larger uncertainty in survival parameters for out-of-hospital cardiac arrest compared to in-hospital.

Our results are comparable with the only other model-based economic evaluation identified in our economic evidence review, the cost-effectiveness analysis by St-Onge et al.[49] Their reported range of ICER ($/LYGs) was $7,185 for their reference survival assumptions and $34,311 using their pessimistic survival assumptions. Our computed ICERs ($18,722/LYG and $28,782/LYG) fall within this range.

Our calculated incremental cost for ECPR for cardiac arrest is also comparable to that reported in another Canadian health technology assessment.[25] Our calculated extra cost for initial care (up to hospital discharge) with ECPR versus standard care was $15,791 ($39,622 − $23,831), compared to their reported 3-day cost of $18,060. However, both our estimates are much lower than the costs reported in the literature for in-hospital cardiac arrest (see Harvey et al[77] for a summary). The main reason for this considerable difference is that many of the studies reporting higher cost also considered costs related to treatment of the underlying cause of cardiogenic shock or cardiac arrest and, in some studies, costs related to destination therapies.

Strengths and Limitations

Our work is the only model-based economic evaluation of ECPR for cardiac arrest with stratified results for both in- and out-of-hospital settings. We used the best available and most relevant evidence to parameterize our model. Our work is also the first to consider the potential gain in organ donation as an outcome in the economic evaluation of ECPR, and we report this separately for in- and out-of-hospital cardiac arrest.

Although we performed extensive sensitivity analyses to explore the variations of ICERs under changing parameter values, our results might not be generalizable to settings in which costs are very different from those we used.

A limitation of our analysis is our inability to follow patients during their treatment for underlying causes of cardiac arrest. We made simplifying assumptions that patients in the intervention and comparator groups would receive similar treatments. In addition, we roughly estimated the costs of long-term follow-up. In reality, these values may be different for subgroups of patients who all receive ECPR but then follow various long-term pathways.

Conclusions

Our primary economic analysis shows that ECPR may be cost-effective compared with conventional CPR for both in-hospital and out-of-hospital cardiac arrest in adults.

BUDGET IMPACT ANALYSIS

Research Questions

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding venoarterial extracorporeal membrane oxygenation (ECMO) in Ontario for adults (age ≥ 18 years):

- With cardiogenic shock that is refractory to conventional medical management?
- With cardiac arrest that is refractory to conventional cardiopulmonary resuscitation (CPR)?

Methods

Analytic Framework

We estimated the budget impact of ECMO for cardiogenic shock or cardiac arrest using the cost difference between two scenarios: (1) the current scenario, which is the current clinical practice with limited use of ECMO for cardiogenic shock funded through hospital global budgets and (almost) no use of ECMO for cardiac arrest, and (2) the new scenario, which is the anticipated clinical practice with public funding for routine use of ECMO for cardiogenic shock and cardiac arrest. Figure 15 presents the budget impact model schematic.

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. In sensitivity analyses we explored how the results are affected by varying input parameters and model assumptions.

The secondary health economist conducted formal internal validation. This included checking for errors and accuracy of parameter inputs and equations.[52]

When discussing the use of ECMO for cardiac arrest, we refer to it as extracorporeal cardiopulmonary resuscitation (ECPR).

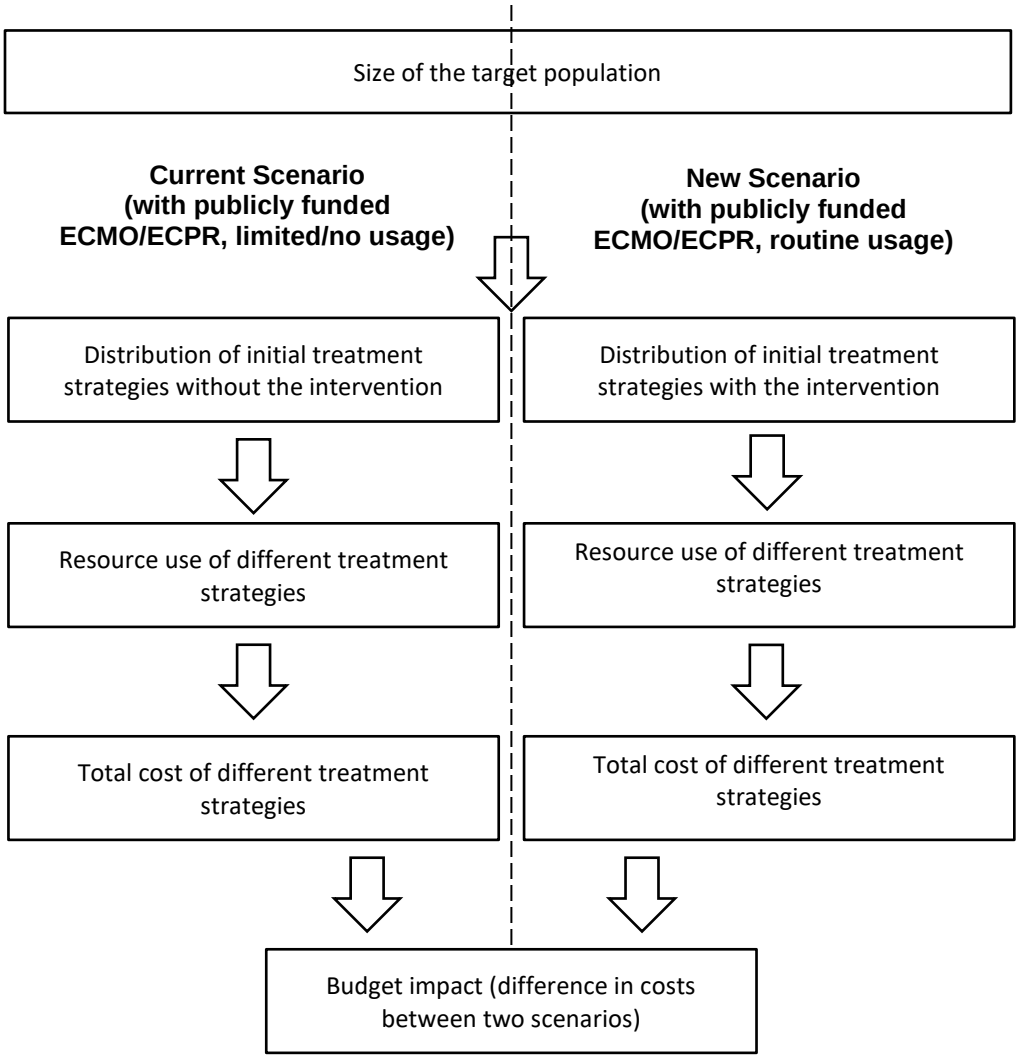

Figure 15: Schematic Model of Budget Impact

Abbreviations: ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation.

Key Assumptions

- We applied all assumptions used in our primary economic evaluation
- The interventions are offered in selected highly specialized centres, with existing trained specialists and staff. We also assumed these centres already own most of the reusable equipment to conduct ECMO or ECPR. Therefore, we did not consider an upfront training cost or initial capital cost for reusable equipment and, instead, distributed those costs among all patients along the time horizon of capital equipment's lifecycle
- For patients with cardiogenic shock, we considered costs only until hospital discharge, including the cost of complications. This was because the comparative evidence currently available did not allow us to quantify costs beyond the initial hospital stay or for the years following hospital discharge. However, we did not consider any costs not directly related to the use of ECMO and assumed these would be the same for both the ECMO and standard care groups

- As we did for cardiac arrest in our primary economic evaluation, and because of a lack of comparative evidence, we set a minimal length of stay in intensive care (ICU), equivalent to the duration of ECPR use, for patients with cardiogenic shock in both the intervention and comparator groups

Target Population and Current Intervention Mix

Extracorporeal Membrane Oxygenation for Cardiogenic Shock

The eligible population consists of people with any circulatory condition leading to an episode of refractory cardiogenic shock. We broadly divided these indications into three categories:

- **Nonsurgical**—This includes patients with myocardial infarction, infective endocarditis, chronic/dilated/hypertrophic/ischemic/peripartum cardiomyopathy, pulmonary embolism, septic shock, chronic/acute heart failure, or arrhythmia, all when leading to cardiogenic shock. Some of these patients can be expected to recover using medications, but some may need more invasive surgical procedures for treatment of underlying cause
- **Postcardiotomy**—This includes patients who have had any heart-related surgery, except heart transplant, resulting in the need for temporary support for cardiac function while they recover
- **Post–heart transplant**—This includes patients who cannot be weaned from the heart-lung machine following heart transplantation or those who develop complications shortly after and need temporary support. These people either recover after a short period of support or they may need subsequent surgery, which may be a repeat heart transplant or implantation of a permanent ventricular assist device

Table 15 lists the yearly number of patients in Ontario who were hospitalized for cardiogenic shock, had a cardiac surgery, or received a heart transplant from 2013/14 to 2016/17.

Table 15: Yearly Number of Ontario Patients With Indications Related to Cardiogenic Shock

Year	Nonsurgical[a]	Postcardiotomy[b]	Post–Heart Transplant[a]
2013/14	2,123	7,955	71
2014/15	2,258	8,145	76
2015/16	2,447	8,192	80
2016/17	2,590	8,159	76

[a]Source: IntelliHealth Ontario, Inpatient Discharges database with diagnostic code R570 for cardiogenic shock, and intervention codes 1HY85LAXXK, 1HZ85LAXXK, and 1HZ85LAXXL for heart transplant.
[b]Source: CorHealth Ontario, 2018.[78]

Table 16 gives the yearly number of patients who received ECMO and who had documented cardiogenic shock in Ontario during 2013 to 2017. If we suppose that cardiogenic shock was the reason for using ECMO for these patients, we can approximate a yearly rate of current use per 100,000 adults, as shown in the last column. The annual rate varies from 0.310 to 0.444, with an average of 0.349 ECMO procedures per 100,000 adults per year.

Table 16: Yearly Number of Extracorporeal Membrane Oxygenation Procedures for Cardiogenic Shock in Ontario

Year	ECMO for Cardiogenic Shock[a]	Ontario Population (≥ 18 Years of Age)	ECMO for Cardiogenic Shock per 100,000 Population
2013/14	35	11,001,497	0.318
2014/15	36	11,117,876	0.324
2015/16	35	11,291,050	0.310
2016/17	51	11,490,799	0.444
Average rate over 4 years			0.349

Abbreviation: ECMO, extracorporeal membrane oxygenation.

[a]*Source: IntelliHealth Ontario, Inpatient Discharges database with diagnostic code R570 and intervention code 1LZ37GPQM.*

Table 17 lists the predicted number of patients in Ontario who would receive ECMO for cardiogenic shock in the next 5 years if we continue with current practice (based on the average rate derived in Table 16).

Table 17: Predicted Yearly Number of Extracorporeal Membrane Oxygenation for Cardiogenic Shock in Ontario, Continuing Current Practice

Year	ECMO for Cardiogenic Shock per 100,000 Population	Ontario Population (≥ 18 Years of Age)	ECMO for Cardiogenic Shock
2019	0.349	11,908,691	42
2020	0.349	12,083,325	42
2021	0.349	12,242,663	43
2022	0.349	12,389,935	43
2023	0.349	12,535,981	44

Abbreviation: ECMO, extracorporeal membrane oxygenation.

To approximate the number of patients in Ontario expected to be eligible for ECMO in the next 5 years if the procedure becomes routine (our new scenario), we reviewed the literature for typical conversion rates for the indications reported in Table 15. A conversion rate calculates the following:

$$\frac{\text{Number of Patients With Indication}}{\text{Number of Patients in Numerator Eligible to Receive ECMO}} \times 100$$

Based on U.S. data reported in Strom et al[79] for 2013 to 2014, we approximated that 4% of nonsurgical cardiogenic shock cases could become refractory to standard treatment and eligible for ECMO. To estimate the number of ECMO procedures for cardiogenic shock subsequent to cardiac surgery and heart transplant, we used the rates of 0.3% and 6.6%, respectively, reported in Borisenko et al.[80] These are the percentages of people who had (or were about to have) an episode of cardiogenic shock and received ECMO, from those who had cardiac surgery or a heart transplant. Table 18 shows the predicted eligible numbers for each indication and the annual totals. For these estimates, we extrapolated values in Table 15 into the future using population estimates and then applied these conversion rates.

Table 18: Predicted Yearly Number of Patients With Cardiogenic Shock Eligible for Extracorporeal Membrane Oxygenation in Ontario, Adopting Typical Practice

	ECMO for Cardiogenic Shock			
Year	Nonsurgical CS	Postcardiotomy CS	Post–Heart Transplant CS	Total
2019	100	26	5	131
2020	101	26	5	132
2021	103	27	5	135
2022	104	27	6	137
2023	105	27	6	138

Abbreviations: CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation.

Extracorporeal Cardiopulmonary Resuscitation for Cardiac Arrest

Table 19 shows the approximate number of people who had a cardiac arrest in Ontario from 2013 to 2017, either in the community or while they were already in a hospital. To approximate these values, we first extracted the number of ambulatory patients with documented cardiac arrest and assumed that was the number that occurred out of hospital. We then extracted the total number of recorded cardiac arrests among all hospitalized patients and took that as the total of in- and out-of-hospital cardiac arrests. The difference between this total and the number of out-of-hospital cardiac arrests was taken as the number of in-hospital cardiac arrests.

Table 19: Yearly Number of Cardiac Arrests in Ontario

Year	In-Hospital[a]	Out-of-Hospital[b]
2013/2014	2,169	4,513
2014/2015	2,090	4,577
2015/2016	2,125	4,978
2016/2017	2,094	5,417

[a]*Source: IntelliHealth Ontario, Inpatient Discharges database with diagnostic codes I460 and I469 for total cardiac arrests; and analytical derivation (total cardiac arrests – out-of-hospital).*
[b]*Source: IntelliHealth Ontario, Ambulatory Visits database with diagnostic codes I460 and I469.*

Next, we extrapolated the numbers in Table 19 into the future using averaged population normalized rates, to calculate the yearly number of people expected to experience a cardiac arrest in Ontario from 2019 to 2023 (Table 20). To estimate the proportion who would be eligible for ECPR, we defined “minimal-practice” and “typical-practice” conversion rates from the literature (the percentage of cardiac arrests in which ECPR was used in various studies). For in-hospital cardiac arrest, we combined the difference in survival from three studies that compared ECPR and conventional CPR[30,36,38] (risk difference = 0.1, 0.15, 0.27, respectively) and the rate of ECPR use in those studies (ECPR was used in 15%, 8%, and 6% of cardiac arrests) to calculate a conversion rate of between 0.9% to 2%. This is the proportion of people with in-hospital cardiac arrests who were given ECPR and for whom the comparative benefit was observed. We take the lower bound of 0.9% as the minimal-practice conversion rate (lowest among centres around the world) and the upper bound of 2% as our typical-practice conversion rate (common practice in the United States and United Kingdom). Similarly, for

out-of-hospital cardiac arrest, we used Maekawa et al[34] (risk difference = 0.25, ECPR rate = 13%) to generate a 3.3% typical-practice conversion rate. For our minimal-practice conversion rate for out-of-hospital cardiac arrest, we used 0.6% as reported in the study by Damluji et al.[81] We applied these rates to the predicted number of cardiac arrests, as shown in Table 20.

Table 20: Predicted Yearly Number of Cardiac Arrests Eligible for Extracorporeal Cardiopulmonary Resuscitation in Ontario, Adopting Minimal Practice or Typical Practice

	Cardiac Arrest		ECPR			
			Minimal Practice		Typical Practice	
Year	In-Hospital	Out-of-Hospital	In-Hospital	Out-of-Hospital	In-Hospital	Out-of-Hospital
2019	2,249	5,163	20	31	45	170
2020	2,282	5,239	21	31	46	173
2021	2,313	5,308	21	32	46	175
2022	2,340	5,372	21	32	47	177
2023	2,368	5,435	21	33	47	179

Abbreviation: ECPR, extracorporeal cardiopulmonary resuscitation.

Uptake of the New Intervention and Future Intervention Mix

Extracorporeal Membrane Oxygenation for Cardiogenic Shock

If there were dedicated public funding of ECMO for people with cardiogenic shock, then the use of this procedure will likely increase. We can assume that uptake will gradually increase from the predicted numbers shown in Table 17 for ECMO using current practice toward the maximum numbers of eligible patients that we calculated in Table 18. In our reference case, we set this gradual increase in uptake at 5% annually across the 5 years of our budget impact analysis. In a scenario analysis, we assumed a more aggressive increase, with uptake of ECMO reaching more than 90% of all eligible patients by year 5, following evenly distributed yearly increases.

Table 21 lists the predicted yearly numbers of patients receiving ECMO for cardiogenic shock in the current scenario and in the new scenario (reference case and scenario analyses).

We also considered the possibility that uptake could increase even more quickly, reaching 90% in 3 years rather than 5. Appendix 8, Table A9, shows the predicted number of patients with cardiogenic shock who would receive ECMO versus standard care under this escalated uptake.

Table 21: Predicted Yearly Number of Patients With Cardiogenic Shock Receiving Extracorporeal Membrane Oxygenation or Standard Care in Ontario, Among Eligible Patients

Year	Total Eligible for ECMO	Current Scenario		New Scenario	
		ECMO, n (Uptake)	Standard Care, n	ECMO, n (Uptake)	Standard Care, n
Reference case: annual 5% increase in uptake					
2019	131	42 (32.1%)	89	49 (37.4%)	85
2020	132	42 (31.8%)	90	56 (42.4%)	81
2021	135	43 (31.9%)	92	64 (47.4%)	78
2022	137	43 (31.4%)	94	72 (52.4%)	74
2023	138	44 (31.9%)	94	73 (57.4%)	70
Scenario analysis: aggressive uptake, reaching 90% by year 5					
2019	131	42 (32.1%)	89	58 (44.3%)	73
2020	132	42 (31.8%)	90	74 (56.1%)	58
2021	135	43 (31.9%)	92	93 (68.9%)	42
2022	137	43 (31.4%)	94	111 (81.0%)	26
2023	138	44 (31.9%)	94	129 (93.5%)	9

Abbreviation: ECMO, extracorporeal membrane oxygenation.

Extracorporeal Cardiopulmonary Resuscitation for Cardiac Arrest

For cardiac arrest, the current practice in Ontario does not include ECPR. If that changes with the availability of dedicated public funding, we can reasonably expect the uptake of this procedure to increase until it reaches the predicted numbers for either minimal or typical practice, as described above and shown in Table 20.

Similar to our analysis for cardiogenic shock, we considered two different ways that uptake of ECPR might increase. Our reference case used an annual 5% increase in uptake, while a scenario analysis assumed uptake would reach 90% of all eligible patients by year 5. However, for this more aggressive scenario, we assumed that uptake would reach the minimal-practice values (see Table 20) in the first year and then move toward typical-practices values over the remaining years.

Tables 22 and 23 list the predicted yearly number of patients receiving ECPR for in- and out-of-hospital cardiac arrest in the current scenario and in both the reference and scenario analyses of the new scenario.

Table 22: Predicted Yearly Number of Patients With In-Hospital Cardiac Arrest Receiving Extracorporeal or Conventional Cardiopulmonary Resuscitation in Ontario, Among Eligible Patients

Year	Total Eligible for ECPR	Current Scenario		New Scenario	
		ECPR, n	Standard Care (CCPR), n	ECPR, n (Uptake)	Standard Care (CCPR), n
Reference case: annual 5% increase in uptake					
2019	45	0	45	20 (44.4%)	25
2020	46	0	46	23 (49.4%)	23
2021	46	0	46	25 (54.4%)	21
2022	47	0	47	28 (59.4%)	19
2023	47	0	47	30 (64.4%)	17
Scenario analysis: aggressive increase in uptake, reaching 90% by year 5					
2019	45	0	45	20 (44.4%)	25
2020	46	0	46	27 (58.7%)	19
2021	46	0	46	32 (69.6%)	14
2022	47	0	47	39 (83.0%)	8
2023	47	0	47	44 (93.6%)	3

Abbreviations: CCPR, conventional cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation.

Table 23: Predicted Yearly Number of Out-of-Hospital Cardiac Arrest Patients Receiving Extracorporeal or Conventional Cardiopulmonary Resuscitation in Ontario, Among Eligible Patients

Year	Total Eligible for ECPR	Current Scenario		New Scenario	
		ECPR, n	Standard Care (CCPR), n	ECPR, n (Uptake)	Standard Care (CCPR), n
Reference case: annual 5% increase in uptake					
2019	170	0	170	31 (18.2%)	139
2020	173	0	173	40 (23.2%)	133
2021	175	0	175	49 (28.2%)	126
2022	177	0	177	59 (33.2%)	118
2023	179	0	179	68 (38.2%)	111
Scenario analysis: aggressive increase in uptake, reaching 90% by year 5					
2019	170	0	170	31 (18.2%)	139
2020	173	0	173	63 (36.4%)	110
2021	175	0	175	96 (54.9%)	79
2022	177	0	177	130 (73.4%)	47
2023	179	0	179	164 (91.6%)	15

Abbreviations: CCPR, conventional cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation.

Resources and Costs

Table 24 shows costs included in our analysis for the use of ECMO for cardiogenic shock and cardiac arrest. For cardiac arrest, we ran our primary economic evaluation without discounting to find the yearly costs per patient (Table 24). For cardiogenic shock, we used a simplified model that only considers costs related to treatment received during the first hospitalization period (application of ECMO and treatment for complications). Therefore, all costs for patients with cardiogenic shock are incurred in the first year (Table 24). Tables 25 and 26 list the values we used for duration of ECMO, cohort age, and rates of complications for cardiogenic shock.

Table 24: Undiscounted Yearly Costs for Patients With Cardiogenic Shock or Cardiac Arrest Receiving Extracorporeal Membrane Oxygenation or Standard Care in Ontario

Year After Initial Episode of Cardiogenic Shock or Cardiac Arrest	Undiscounted Yearly Cost, $[a]					
			Cardiac Arrest			
	Cardiogenic Shock		In-Hospital		Out-of-Hospital	
	ECMO	Standard Care	ECPR	Standard Care	ECPR	Standard Care
1	39,622	23,831	33,627	18,287	33,231	19,415
2			2,627	1,331	3,023	2,130
3			2,309	1,169	2,939	2,071
4			2,030	1,027	2,858	2,013
5			1,784	902	2,780	1,957

Abbreviations: ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation.
[a]In 2019 Canadian dollars.

Table 25: Summary Estimates Associated with Extracorporeal Membrane Oxygenation for Cardiogenic Shock

Model Parameters	Value	Range	Reference
Duration of ECMO, days, mean (CI)	6.23 (5.89, 6.57)	2–29	ELSO,[53] 2014–2016
Cohort age, years, mean (SE)	51.31 (3.51)	18–80	IntelliHealth Ontario, 2014–2017

Abbreviations: CI, confidence interval; ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; SE, standard error.

Table 26: Risk of Complications With Extracorporeal Membrane Oxygenation for Cardiogenic Shock

Adverse Event/Complication	Risk Probability, Mean (SE)	Reference
Mechanical failure (oxygenator/pump)	0.089 (0.003)	ELSO,[53] 1992–2016
Bleeding of (surgical/cannulation) site	0.192 (0.004)	
Culture proven infection	0.128 (0.003)	
Limb ischemia	0.036 (0.002)	
Limb amputation	0.005 (0.001)	

Abbreviations: ELSO, Extracorporeal Life Support Organization; SE, standard error.

Analysis

In our analysis, we calculate the budget required for publicly funding the routine use of ECMO/ECPR for refractory cardiogenic shock or refractory cardiac arrest in Ontario over the next 5 years (2019–2023), based on the estimated number of procedures. We also calculate the annual and 5-year budget impact as the difference between the costs of ECMO or ECPR and standard treatment. We include the cost of initial treatment at first hospitalization, cost of complications (adverse events), and the cost of long-term care for survivors.

In our reference case we conducted our analysis with a conservative increase in uptake over a 5-year implementation period, while in a scenario analysis we used more aggressive uptake rates.

We also report the potential gain in organ donation with the use of ECPR for cardiac arrest. For this part of the analysis, we used the results of our primary economic evaluation (see Table 13) and the eligible number of patients in the current and new scenarios.

Results

Table 27 shows the yearly cost, 5-year total, and budget impact of the new scenario (reference case and scenario analyses), compared with current practice in Ontario (limited use of ECMO for patients with cardiogenic shock and no use of ECPR to stabilize patients with cardiac arrest).

In the reference case, the yearly budget impact of the new scenario increases for all cardiac indications: from about $110,000 to $553,000 for cardiogenic shock, from $300,000 to $566,000 for in-hospital cardiac arrest, and from $430,000 to $1.1 million for out-of-hospital cardiac arrest. For cardiogenic shock, the increase is due to the increasing number of patients expected to be eligible for ECMO (see Table 21), but for cardiac arrest the increase is also affected by follow-up costs, as well as by the rise in the number of patients (see Tables 22, 23, and 24). Overall, the 5-year budget impact for publicly funding all indications would cost an additional $7.6 million.

Table 27: Total Cost and Budget Impact in Ontario for Adoption of Extracorporeal Membrane Oxygenation Versus Standard Care for Cardiogenic Shock or Cardiac Arrest

	Total Cost, $[a]					
Scenario	**2019**	**2020**	**2021**	**2022**	**2023**	**5-Yr Total**
Cardiogenic shock						
Current practice	3,785,092	3,808,924	3,896,208	3,943,870	3,983,492	19,417,586
Reference: conservative uptake	3,895,627	4,029,993	4,227,812	4,401,799	4,536,165	21,091,396
Budget impact	**110,535**	**221,069**	**331,604**	**457,929**	**552,673**	**1,673,811**
Scenario: aggressive uptake	4,037,743	4,314,225	4,685,741	5,017,635	5,325,699	23,381,043
Budget impact	**252,651**	**505,301**	**789,533**	**1,073,765**	**1,342,207**	**3,963,457**
In-hospital cardiac arrest						
Current practice	822,929	901,108	955,057	1,020,736	1,063,682	4,763,511
Reference: conservative uptake	1,129,727	1,279,842	1,391,160	1,528,932	1,629,369	6,959,028
Budget impact	**306,798**	**378,734**	**436,103**	**508,197**	**565,687**	**2,195,517**
Scenario: aggressive uptake	1,129,727	1,341,201	1,503,722	1,711,302	1,870,374	7,556,326
Budget impact	**306,798**	**440,093**	**548,665**	**690,566**	**806,692**	**2,792,815**
Out-of-hospital cardiac arrest						
Current practice	3,300,589	3,720,909	4,118,126	4,509,632	4,895,640	20,544,895
Reference: conservative uptake	3,728,887	4,301,232	4,857,756	5,429,470	5,989,667	24,307,013
Budget impact	**428,299**	**580,324**	**739,630**	**919,838**	**1,094,027**	**3,762,117**
Scenario: aggressive uptake	3,728,887	4,619,002	5,527,649	6,472,356	7,439,665	27,787,559
Budget impact	**428,299**	**898,094**	**1,409,523**	**1,962,724**	**2,544,025**	**7,242,664**
Cardiogenic shock + in-hospital cardiac arrest + out-of-hospital cardiac arrest						
Current practice	7,908,610	8,430,940	8,969,390	9,474,238	9,942,814	44,725,992
Reference: conservative uptake	8,754,241	9,611,067	10,476,727	11,360,201	12,155,201	52,357,437
Budget impact	**845,631**	**1,180,127**	**1,507,337**	**1,885,964**	**2,212,387**	**7,631,446**
Scenario: aggressive uptake	8,896,357	10,274,428	11,717,112	13,201,293	14,635,738	58,724,927
Budget impact	**987,747**	**1,843,488**	**2,747,722**	**3,727,056**	**4,692,923**	**13,998,936**

[a]In 2019 Canadian dollars.

In Table 28 we report the results for our analysis of the potential gain in organ donations following cardiac arrest, if ECPR were adopted as routine practice for eligible patients. The yearly increase in gain is a result of increased uptake of ECPR. However, the gains are more notable for out-of-hospital cases, for two reasons: more out-of-hospital patients are expected to receive ECPR and the per-patient gain is larger (see Table 13 in our primary economic evaluation).

With the adoption of ECPR for adults with refractory cardiac arrest, Ontario would gain, on average each year, approximately 2 additional successful organ donors among people who do not survive an in-hospital cardiac arrest, and an additional 10 donors among those who do not survive an out-of-hospital cardiac arrest.

Table 28: Total Number of and Gain in Organ Donors With Adoption of Extracorporeal Versus Conventional Cardiopulmonary Resuscitation for Cardiac Arrest

	Total Donors, n[a]					
Scenario	**2019**	**2020**	**2021**	**2022**	**2023**	**5-Yr Total**
In-hospital cardiac arrest						
Current practice	0.50	0.51	0.51	0.52	0.52	2.55
Reference: conservative uptake	2.33	2.61	2.79	3.08	3.26	14.07
Gain	**1.83**	**2.10**	**2.29**	**2.56**	**2.74**	**11.52**
Scenario: aggressive uptake	2.33	2.98	3.43	4.08	4.54	17.36
Gain	**1.83**	**2.47**	**2.93**	**3.56**	**4.02**	**14.81**
Out-of-hospital cardiac arrest						
Current practice	9.53	9.69	9.81	9.92	10.03	48.98
Reference: conservative uptake	16.22	18.33	20.39	22.66	24.72	102.32
Gain	**6.70**	**8.64**	**10.58**	**12.74**	**14.69**	**53.34**
Scenario: aggressive uptake	16.22	23.30	30.54	38.00	45.45	153.51
Gain	**6.70**	**13.61**	**20.73**	**28.08**	**35.42**	**104.53**

[a]Although the real gain (the increase in the number of organ donors) is always a whole number, for comparative purposes we report the averages to two decimal places.

Discussion

Venoarterial (VA) ECMO is the only option currently available to escalate care for people in refractory cardiac arrest, and it is one of several options for refractory cardiogenic shock. Other options for cardiogenic shock include temporary percutaneous ventricular assist devices (VAD) such as Impella and TandemHeart. However, a 2017 health technology assessment by Health Quality Ontario showed little or no clinical benefit and large incremental costs with Impella for people with cardiogenic shock[82] and, as a result, its routine use for this purpose has been discouraged in Ontario. The TandemHeart device has been used in very limited numbers in recent years, but the complexity of the operation and potential complications along with the high cost of the device prevented its diffusion.

Currently, venovenous (VV) ECMO is routinely used in Ontario for refractory respiratory failure. Considering that the equipment needed for VV ECMO is the same for VA ECMO, and the applications are not very different, we can say that many centres in Ontario already have the equipment and expertise to use ECMO for cardiac indications. Our investigation of Ontario registry data and communications with experts confirm that many centres in Ontario have been doing VV ECMO, but only three centres (University Health Network in Toronto, University Hospital – London Health Sciences Centre, and The University of Ottawa Heart Institute) have been doing VA ECMO at an acceptable minimum volume (more than 5 procedures a year). This limited use of VA ECMO is due to funding limitations, the complexity of managing patients receiving VA ECMO, and lower certainty about the clinical benefits and cost-effectiveness of VA ECMO, which may have been more clearly shown for VV ECMO.[83,84]

Our analysis shows that the routine use of VA ECMO for cardiogenic shock and cardiac arrest would have a low to moderate budget impact in Ontario. As the equipment is already in routine use for respiratory indications, the cost of acquiring the required equipment may be minimal.

Some issues that may need attention in implementation due to their potential budgetary impact are: (1) the need for continual specialized training for personnel involved in the procedure; (2) the need to establish clear, protocols for deciding which patients are appropriate for ECMO and for ending the support when it is declared futile; (3) the need to efficiently share the equipment among its various uses within a hospital (VA ECMO, VV ECMO, and temporary VAD support) and to efficiently switch between modalities when necessary; (4) the need for protocols to take advantage of potential for increased organ donation; and (5) the potential need for additional capital (e.g. ward and ICU beds) and human resource requirements (e.g. perfusionists).

Strengths and Limitations

There are several strengths to this analysis. We used Ontario-specific costs for most items. We also explored various scenarios for increased uptake in the use of ECMO. We used published literature and Ontario registries to inform estimates of the number of people eligible for ECMO and ECPR. We also estimated the gain in organ donation by people who receive ECPR for cardiac arrest but do not survive. In each case, we used the best and most relevant evidence available. Our method for estimating the size of eligible populations is generalizable to other settings.

However, our cost and budget impact results cannot be generalized to settings where equipment costs or personnel fees are considerably different from those we used.

As in our primary economic evaluation, we were not able to include the costs of treatment for underlying causes and, therefore, our total costs may be underestimated. We assumed that such costs would likely cancel out in the budget impact, but in reality there may be differences in treatment costs for people who are or are not eligible to receive ECMO for cardiac indications. However, the poor quality of comparative evidence would not have allowed us to estimate the direction (saving or spending) of this difference, if we had been able to consider it.

Conclusions

In Ontario, the current uptake of ECMO for cardiogenic shock is lower than internationally reported for jurisdictions with similar estimates of eligible patients, and the use of ECPR for cardiac arrest is very limited. If dedicated public funding for ECMO or ECPR were to become available, we estimate a total budget impact over the next 5 years of about $845,000 to $2.2 million per year.

PATIENT PREFERENCES AND VALUES

Objective

The objective of this analysis was to explore the underlying values, needs, preferences, and priorities of those who have lived experience with extracorporeal membrane oxygenation (ECMO) for cardiac indications, either for the treatment of cardiogenic shock or as extracorporeal cardiopulmonary resuscitation (ECPR) for the treatment of cardiac arrest.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat the health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[85-87] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Methods

Engagement Plan

The engagement plan for this health technology assessment focused on consultation to examine the lived experiences of people who have received ECMO and those of their family members. We engaged people via interviews by phone.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people who have received ECMO as well as those of their families.[88] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of a confidential one-on-one interview methodology.

Participant Outreach

We used an approach called purposive sampling,[89-92] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations, including CorHealth Ontario and Trillium Gift of Life Network, as well as clinical experts who have cared for patients receiving ECMO. We asked each to spread the word about this engagement activity and our desire to speak to patients and family members about their experiences with ECMO.

Inclusion Criteria

We sought to speak with adults with lived experience of ECMO and with family members. We sought people who had received ECMO for cardiogenic shock or for cardiac arrest.

Exclusion Criteria

As per the scope of this health technology assessment, we only sought to interview adults, 18 years of age or older.

Participants

We spoke to eight people—four patients and four family members—with direct experience of ECMO. All were familiar with ECMO as a rescue therapy for cardiogenic shock, rather than for cardiac arrest. Clinical experts reported that the use of ECMO for cardiac arrest is not common in Ontario.

Approach

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and, if requested, in a letter of information (Appendix 9). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted 15 to 40 minutes. The interview was semi-structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[93] Questions focused on the health condition of the patient leading up to the use of ECMO, decision-making values and preferences when it came to choosing to receive ECMO, and their overall experiences and impressions of the technology. Where applicable, we spoke about their perceptions of the benefits and limitations of ECMO. See Appendix 10 for our interview guide.

Data Extraction and Analysis

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[94,95] We used the qualitative data analysis software program NVivo[96] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight important themes in the use of ECMO from the patient and family perspective.

Results

Health Conditions Requiring Extracorporeal Membrane Oxygenation

ECMO is a rescue therapy used to stabilize patients who are hemodynamically compromised, meaning their body is not able to circulate blood properly. ECMO is not a treatment or cure, but rather it temporarily substitutes for the work of the heart and lungs, allowing them to rest until the problem that is causing reliance on ECMO is reversed. The participants we interviewed emphasized the serious nature of the use of this device and spoke of the underlying, life-threatening health conditions that necessitated its use.

Each patient encountered ECMO while receiving acute care in a hospital. Several participants required ECMO in the context of a heart or lung transplant. In two cases, we spoke with family members of people who had received ECMO but nevertheless subsequently died. Overall, the nature of the illnesses leading to the use of ECMO were varied, though all were serious:

> *They had to do open heart surgery … But he was at high risk for bleed out. So for that reason they put him on the heart-lung machine.*

> *I think I was just so sick and they were like, "Her heart is going to fail during this operation if we don't put her on the ECMO." So they did that ahead of time, during the procedure, then I was on it for five days after.*

Information and Perceptions About Extracorporeal Membrane Oxygenation

Despite the varied nature of the conditions requiring the use of ECMO, there were some similarities in the information participants received about the device and their perceptions of its use. For the most part, participants were not familiar with ECMO before their health care team told them they might need this procedure. It was not well known as a life-saving device, and several participants described it as a "heart–lung machine" rather than by the clinical name. Some participants, with a background in health care, were distantly familiar with the device but unsure of its overall purpose or the criteria for using it:

> *I had absolutely no idea what [ECMO] was. I didn't even know I was on it at first.*

> *And I would say probably everybody in our family kind of knew, but you have this idea but you don't really know how it's done or what it looks like until you actually see it. I had never seen it myself. I had heard about it, especially in Ottawa here, because of the Heart Institute, I know that that's something they've done with the heart transplants, but I did not know much more about it.*

> *I remember vaguely that with ECMO you wanted to be off it as soon as you can, because it can affect oxygen to your brain … which is why it's a great machine temporarily to help support, but not sustain.*

Conversations and Decision-Making Surrounding Extracorporeal Membrane Oxygenation

The serious nature of the health conditions that necessitated the use of ECMO meant that participants typically learned about the procedure from health care professionals in the midst of their hospital care, prior to surgery or while being treated in an intensive care unit.

It was during these interactions that physicians discussed with them the nature of ECMO, its potential impact, and the criteria for its use. These discussions were unique to each patient, given their varied health conditions and the urgency of the situation. And participants did not describe the information they received in a consistent way. In some cases, the patient was directly informed about ECMO and provided formal consent. In other cases, it was the family member who was consulted and the process for consent was less clear. Some participants were unable to recall the exact nature of the discussions with health care providers, given the

stress and high emotions of the circumstances. Some participants recalled a very quick conversation, with a health provider in an emergency-like atmosphere, without remembering much about the degree of information provided:

> *The hospital knew what I wanted though; they knew if there was any sort of chance, I wanted it … They knew my situation and stuff, so I don't ever remember having a conversation with them about ECMO, but we may have.*

> *Well, before they put the ECMO in, they came out to the, I don't know, the waiting room I guess it was, and there was not even a two-minute conversation, and they came out and saying, "Her heart's not beating. You have a choice, either you let it be or we put her on the ECMO machine and take that chance. If her heart doesn't start beating [on its own] within seven days, then she'll be gone."*

Some participants reflected on the emotions of fear and uncertainty they experienced when they had to consider the potential use of ECMO. Generally, however, this was part of their overall fear about the serious nature of their medical condition and the fact that they needed a stabilizing intervention; it was not specific to the ECMO device itself:

> *As it was explained, yes, it was a life-saving method, but basically you're in suspended animation. You're basically, you know, dead. Alive, but dead, if you know what I mean. That's how I remember it anyway. It's like whoa, it's pretty scary.*

> *He'll never tell you how afraid he was [of using ECMO]. I'm telling you.*

> *So, what was explained to us was some of the standard risks and benefits and it was quite an eye-opener, but you also were convinced that it was a life-saving necessity if they indeed have to go with the ECMO.*

When relating their experiences during critical medical circumstances, participants emphasized that the decision to use ECMO was fundamentally a medical decision, rather than a simple patient choice. Acknowledging their own limitations to understand the full scope and implications of the use of ECMO, participants reported that they relied on the physicians to provide them the assurance and confidence that this decision was the right one for themselves or their loved one. Some participants reflected they were comfortable with trusting their physicians to make the correct and logical decision regarding their health:

> *Whereas me, all I want to know is, "Can you do this operation? Yes?" That's good enough for me. Because if you tell me too much beforehand, then I'll just fester on it.*

> *So it's overwhelming, but they're presenting it as the next logical thing to use in situations like this. I mean it was a pretty easy decision. I don't [think] it was presented with a lot of downsides, given the state that she was in.*

> *I don't think they asked, they didn't ask me about it. You find that you believe that they will make the best decisions medically.*

> *It was critical enough that it [ECMO] was done inside the operating suite. There was really no time to consult anyone. My directive, for what it was worth, going into the operation is "Do whatever the hell you need to do." Obviously that's not the way they phrased it, but, you know.*

Lived Experience With Extracorporeal Membrane Oxygenation

Participants were generally unable to describe the experience of using ECMO. Some mentioned vague sensations similar to drowning or feeling pressure, but these reports were not consistent among participants. The critical medical circumstances often required the use of other medical devices at the same time, such as intravenous lines or intubations, and patients could not generally separate the sensation of using ECMO versus other devices. Additionally, patients were medically sedated during ECMO, furthering their inability to recall the experience:

> *The very first memory I had was waking up feeling like I was literally drowning, like I was just literally drowning, with a bunch of people around me doing so many things. Again, my recollection of this can be extremely tainted, because I just woke up, I'm still under some medication, you know.*

> *I don't think that he remembers much, because I did ask him about that. He mentioned pain. He mentioned that being cold was painful. I do remember him saying that. I never pursued it past that.*

> *Also, not only did I have ECMO, but I was intubated and had a lot of their machines at the same time. So this memory of pain is just the intubation. But I do remember feeling pressure and they had to keep me sedated as well.*

For family members, the appearance of the ECMO device being used on their loved one had an impact. They expressed surprise and concern about the nature of the device, specifically the size of the device and its multiple large tubes:

> *Even though I'm a nurse and I've worked in dialysis, so I'm used to seeing large tubes with large amounts of blood going through, to actually see that, it's yeah, I would say it's startling. It's kind of scary because it a very large tube, it's quite big.*

Participants were unable to comment substantially on the overall safety of the device. One person reported receiving a notice several months later that the ECMO device used in their care may have used compromised air. However, this did not result in further health complications or interventions.

For the most part, the interviews did not shed light on the effectiveness of the ECMO device. The two family members of patients who had since died did not view ECMO as the cause of their family member's passing. Rather it was one of many tools used in an attempt to stabilize their loved one, who had serious underlying health conditions. Participants who were hemodynamically unstable, received ECMO, and recovered were naturally grateful and viewed the effectiveness of the device positively. Use of ECMO, among other medical interventions, had saved their lives. However, there exists a natural bias in this population of patients and family members, given their successful experience with ECMO:

> *And in retrospect, I mean, I suppose it was the right decision, because like I said, I'm here talking to you, aren't I?*
>
> *For me, the particular device, when I know what it can do, I think it's amazing that they actually do have something that can breach whatever the body needs and do it for periods while they take care of other parts. Because otherwise the person wouldn't live. I mean, without the ECMO and in certain circumstances, you wouldn't make it through.*
>
> *So I was on this ECMO thing and, obviously it worked, because I'm talking to you now from my home.*

In general, participants expressed appreciation for the ECMO device and, on a larger scale, appreciation for the health care practitioners who cared for them and for the health care system as a whole. Participants viewed ECMO as a life-saving device for which they were grateful and saw value in a health care system that makes such resources available:

> *I remember just being very overwhelmed about the support that was there and the fact that she was able to get through this in a way—in any other country, at any other time—[that] would have been impossible.*
>
> *I remember having these conversations about how, in a certain way, [the ECMO is] sort of this reflection of the Canadian system, about how much time and resources are spent on one person and all the measures that are taken for that.*

Discussion

Due to the relatively low use of ECMO and the critical medical conditions that may necessitate its use, our patient engagement was fairly limited. Most participants were connected with lung or heart transplant programs, but others had suffered sudden, acute hemodynamic instability, resulting in the use of ECMO. We were unable to speak to any patients or family members with experience with ECMO used as ECPR for cardiac arrest.

Participants included both patients and family members, allowing for diversity of viewpoints about this technology. Participants were able to speak to their health conditions which led to the use of ECMO and were able to report on the decision-making process. Often, this decision was placed in the hands of trusted health care professionals at a critical health juncture.

Generally, selection bias in our participants reflected the successful use of ECMO and its positive impact. We interviewed two family members of patients who had subsequently died, but their deaths were not related to the use of ECMO.

Participants were able to comment in general on the use of the device and the positive impact it had on their acute medical condition. But due to the typically emergency situations in which ECMO was needed, often requiring sedation and the use of other devices simultaneously, participants had difficulty clearly remembering the experience.

Conclusions

Participants encountered ECMO while in a life-threatening medical condition, which limits their ability to assess its impact or provide clear impressions of the device. In the decision to receive the procedure, participants generally relied on the expertise and judgment of health care providers. Patient input in the decision-making was limited and variable. Overall, participants were grateful for the availability of ECMO as a life-saving device and its ability to help stabilize their acute medical condition.

CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT

For adults treated for refractory cardiac arrest, venoarterial extracorporeal membrane oxygenation (ECMO) used as extracorporeal cardiopulmonary resuscitation (ECPR) may improve 30-day survival, but we are very uncertain (GRADE: Very Low). ECPR may improve long-term survival (GRADE: Low). ECPR may improve 30-day favourable neurological outcome, but we are very uncertain (GRADE: Very Low). ECPR likely improves long-term favourable neurological outcome (GRADE: Moderate). ECPR may be associated with a significant increase in treatment-related complications, such as leg ischemia/malperfusion, bleeding, or hematoma with need for transfusion, compared with conventional cardiopulmonary resuscitation (GRADE: Low).

For adults treated for refractory cardiogenic shock, ECMO may not result in a difference in 30-day survival compared with percutaneous ventricular assist devices, but we are very uncertain (GRADE: Very Low). ECMO may improve 30-day survival compared with intra-aortic balloon pump, but we are very uncertain (GRADE: Very Low). ECMO may be associated with worsened 30-day and long-term survival compared with nonpercutaneous ventricular assist devices, but we are very uncertain (GRADE: Very Low). ECMO may be associated with a significant increase in systemic inflammatory response compared with ventricular assist devices in patients with postcardiotomy cardiogenic shock, but we are very uncertain (GRADE: Very Low).

Existing cost-effectiveness studies had inconsistent and inadequate results, which prevented us from making any conclusion about ECMO for adults with cardiogenic shock or cardiac arrest. The most notable limitation of almost all studies was the incomparability of their intervention and comparator populations. Therefore, we conducted a primary economic evaluation, which shows that ECPR may be cost-effective compared with conventional CPR for both in-hospital and out-of-hospital cardiac arrest in adults. We did not include ECMO for cardiogenic shock in our model because of the very low quality of evidence available for this indication.

In Ontario, the current uptake of ECMO for cardiogenic shock is lower than internationally reported for jurisdictions with similar estimates of eligible patients, and the use of ECPR for cardiac arrest is very limited. If dedicated public funding for ECMO/ECPR were to become available, we estimate a total budget impact over the next 5 years of about $845,000 to $2.2 million per year.

The patients and family members we interviewed had encountered ECMO while in life-threatening medical circumstances, limiting their ability to assess its impact or provide clear impressions of the procedure. In the decision to receive ECMO, participants generally relied on the expertise and judgment of health care providers. Patient input in the decision-making was limited and variable. Overall, participants were grateful that ECMO was available as a life-saving device and able to help stabilize their or their loved one’s acute medical condition.

ABBREVIATIONS

CAD	Canadian dollar
CI	Confidence interval
CPR	Cardiopulmonary resuscitation
ECMO	Extracorporeal membrane oxygenation
ECPR	Extracorporeal cardiopulmonary resuscitation
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IABP	Intra-aortic balloon pump
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
LVAD	Left ventricular assist device
LY	Life-year
LYG	Life-year(s) gained
NICE	National Institute for Health and Care Excellence
PCI	Percutaneous coronary intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
pVAD	Percutaneous ventricular assist devices
QALY	Quality-adjusted life-year
ROBINS-I	Risk of Bias in Non-randomized Studies—of Interventions
ROBIS	Risk of Bias Among Systematic Reviews
RR	Relative risk
SD	Standard deviation
TBiVAD	Temporary biventricular assist device
TVAD	Temporary ventricular assist device
USD	United States dollar
VA ECMO	Venoarterial extracorporeal membrane oxygenation
VAD	Ventricular assist device
VV ECMO	Venovenous extracorporeal membrane oxygenation

GLOSSARY

Adverse event	An adverse event is any unexpected problem that happens during or as a result of treatment, regardless of the cause or severity.
Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., its affordability). It is based on predictions of how changes in the intervention mix impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Cardiopulmonary resuscitation (CPR)	Cardiopulmonary resuscitation is a lifesaving technique used when someone's heart or breathing has stopped. It consists of manual chest compression and rescue breathing to restart the heart and restore blood circulation.
Cost-effective	A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Cost-effectiveness acceptability curve	In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic sensitivity analysis. It illustrates the probability of health care interventions being cost-effective over a range of different willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values are plotted on the vertical axis.
Cost-effectiveness analysis	Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a specific type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.
Cost-effectiveness plane	In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

Cost–utility analysis	A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years (QALYs), which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.
Deterministic sensitivity analysis	Deterministic sensitivity analysis is an approach used to explore uncertainty in the results of an economic evaluation by varying parameter values to observe the potential impact on the cost-effectiveness of the health care intervention of interest. One-way sensitivity analysis accounts for uncertainty in parameter values one at a time, whereas multiway sensitivity analysis accounts for uncertainty in a combination of parameter values simultaneously.
Discounting	Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health (Quality) use an annual discount rate of 1.5% for both future costs and future benefits.
Health state	A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.
Incremental cost	An incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost of the intervention by its incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.
Intra-aortic balloon pump (IABP)	An intra-aortic balloon pump is a device used as short-term treatment to help a person's heart pump more blood. The device includes a balloon that is inserted into the aorta, the largest artery leaving the heart. The balloon is set to inflate when the heart relaxes and deflate when the heart contracts, helping the heart pump more blood throughout the body.
Life-years gained (LYG)	Life-years gained is a measure that expresses the additional number of years of life that a person lives as a result of receiving a treatment.

Markov model	A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.
Ministry of Health perspective	The perspective adopted in economic evaluations determines the types of cost and health benefit to include. Ontario Health (Quality) develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).
Monte Carlo simulation	Monte Carlo simulation is an economic modelling method that derives parameter values from distributions rather than fixed values. The model is run several times, and in each iteration, parameter values are drawn from specified distributions. This method is used in microsimulation models and probabilistic sensitivity analysis.
Natural history of a disease	The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.
Probabilistic sensitivity analysis (PSA)	A probabilistic sensitivity analysis (PSA) is used in economic models to explore uncertainty in several parameters simultaneously. It is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.
Quality-adjusted life-year (QALY)	The quality-adjusted life-year is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations so that results can be compared across studies.
Risk difference	The risk difference is the difference in the risk of an outcome occurring between one health care intervention and an alternative intervention.
Risk ratio	A risk ratio is the ratio of two risks (probabilities) that an event or outcome will occur during a specified period.
Scenario analysis	A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.
Sensitivity analysis	Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.
Societal perspective	The perspective adopted in an economic evaluation determines the types of cost and health benefit to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer perspective, patient perspective). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).
Time horizon	In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.
Tornado diagram	In economic evaluations, a tornado diagram is used to determine which model parameters have the greatest influence on results. Tornado diagrams present the results of multiple one-way sensitivity analyses in a single graph.
Utility	Utilities are values that represent people's preferences for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Ventricular assist device (VAD)	A ventricular assist device (VAD) is a small mechanical pump that helps pump blood from the lower chambers of the heart (the ventricles) to the rest of the body. A VAD is used in people who have weakened hearts or heart failure. The most frequently used type is placed in the left ventricle (left ventricular assist device, or LVAD). VADs can be used as temporary, short-term treatment, such as when someone is waiting for a heart transplant, or as permanent, long-term support for someone with heart failure who is not a candidate for a transplant. Implanting a VAD often requires open heart surgery, but the device can also be inserted through the skin (percutaneous).
Willingness-to-pay value	A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: September 20, 2018

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2018>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 19, 2018>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2018 Week 38>, Ovid MEDLINE(R) ALL <1946 to September 19, 2018>

Search strategy:

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1 Shock, Cardiogenic/ (16825)
2 (((cardiogenic or circulatory or cardiac) adj3 shock*) or postcardiotom* or post cardiotom*).ti,ab,kf. (33532)
3 (*Myocardial Infarction/ or Myocarditis/) and acute.ti,ab,kf. (65631)
4 ((acute or fulminant*) adj2 (myocardial infarct* or myocarditi* or heart attack or heart attacks)).ti,ab,kf. (147946)
5 Heart Failure/ and (end stage or endstage or acute or decompensat* or refract*).ti,ab,kf. (62983)
6 (heart failure adj2 (end stage or endstage or acute or decompensat* or refract*)).ti,ab,kf. (39105)
7 exp Intensive Care Units/ (229610)
8 ((intensive care adj (unit* or ward* or department* or bed*)) or ICU or ICUs).ti,ab,kf. (323760)
9 Heart Arrest/ (85316)
10 Out-of-Hospital Cardiac Arrest/ (10711)
11 (((cardiac or cardiopulmonar* or cardio pulmonar* or heart) adj2 arrest*) or asystole*).ti,ab,kf. (90800)
12 or/1-11 (760256)
13 Extracorporeal Membrane Oxygenation/ (26882)
14 ((extracorp* or extra corp*) adj2 (life support* or cardiopulmonar* resuscit* or cardio pulmonar* resuscit* or rescue* or CPR)).ti,ab,kf. (5172)
15 (((extracorporeal or extra corporeal) adj2 membrane adj2 oxygenation*) or ECMO).ti,ab,kf. (25997)
16 (cardiohelp or centrimag or rotaflow or cardiacassist or ((maquet or thoratec) adj6 (oxygenat* or extracorp* or extra corp*))).ti,ab,kf. (892)
17 (ECLS or E CLS or ECPR or E CPR).ti,ab,kf. (3517)
18 Extracorporeal Circulation/ (27372)
19 exp Cardiopulmonary Resuscitation/ (113166)
20 18 and 19 (638)
21 or/13-17,20 (38605)
22 12 and 21 (13976)
23 exp Animals/ not Humans/ (15653215)

24 22 not 23 (7624)
25 Case Reports/ or Congresses.pt. (1961750)
26 24 not 25 (6737)
27 limit 26 to yr="2010 -Current" (4781)
28 limit 27 to english language [Limit not valid in CDSR; records were retained] (4554)
29 28 use medall,cctr,coch,clhta,cleed (2450)
30 cardiogenic shock/ (28422)
31 (((cardiogenic or circulatory or cardiac) adj3 shock*) or postcardiotom* or post cardiotom*).tw,kw. (33961)
32 acute heart infarction/ (66693)
33 myocarditis/ and acute.tw,kw. (8863)
34 ((acute or fulminant*) adj2 (myocardial infarct* or myocarditi* or heart attack or heart attacks)).tw,kw. (149619)
35 acute heart failure/ (17664)
36 (heart failure adj2 (end stage or endstage or acute or decompensat* or refract*)).tw,kw. (39721)
37 exp intensive care unit/ (229275)
38 ((intensive care adj (unit* or ward* or department* or bed*)) or ICU or ICUs).tw,kw. (327316)
39 heart arrest/ (85316)
40 "out of hospital cardiac arrest"/ (10711)
41 (((cardiac or cardiopulmonar* or cardio pulmonar* or heart) adj2 arrest*) or asystole*).tw,kw. (91445)
42 or/30-41 (750147)
43 extracorporeal oxygenation/ (18268)
44 extracorporeal membrane oxygenation device/ (987)
45 ((extracorp* or extra corp*) adj2 (life support* or cardiopulmonar* resuscit* or cardio pulmonar* resuscit* or rescue* or CPR)).tw,kw,dv. (5316)
46 (((extracorporeal or extra corporeal) adj2 membrane adj2 oxygenation*) or ECMO).tw,kw,dv. (26638)
47 (cardiohelp or centrimag or rotaflow or cardiacassist or ((maquet or thoratec) adj6 (oxygenat* or extracorp* or extra corp*))).tw,kw,dv. (1657)
48 (ECLS or E CLS or ECPR or E CPR).tw,kw,dv. (3595)
49 extracorporeal circulation/ (27372)
50 resuscitation/ (121843)
51 49 and 50 (712)
52 or/43-48,51 (37650)
53 42 and 52 (14102)
54 (exp animal/ or nonhuman/) not exp human/ (9993388)
55 53 not 54 (13820)
56 Case Report/ or conference abstract.pt. (7125509)
57 55 not 56 (7645)
58 limit 57 to yr="2010 -Current" (5977)
59 limit 58 to english language [Limit not valid in CDSR; records were retained] (5643)
60 59 use emez (3470)
61 29 or 60 (5920)
62 61 use medall (2300)
63 61 use emez (3470)
64 61 use coch (2)
65 61 use cctr (141)
66 61 use clhta (3)
67 61 use cleed (4)

68 remove duplicates from 61 (4073)

Economic Evidence Search

Search date: September 21, 2018

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2018>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 19, 2018>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2018 Week 38>, Ovid MEDLINE(R) ALL <1946 to September 20, 2018>

Search strategy:

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1 Shock, Cardiogenic/ (16825)
2 (((cardiogenic or circulatory or cardiac) adj3 shock*) or postcardiotom* or post cardiotom*).ti,ab,kf. (33538)
3 (*Myocardial Infarction/ or Myocarditis/) and acute.ti,ab,kf. (65635)
4 ((acute or fulminant*) adj2 (myocardial infarct* or myocarditi* or heart attack or heart attacks)).ti,ab,kf. (147952)
5 Heart Failure/ and (end stage or endstage or acute or decompensat* or refract*).ti,ab,kf. (62985)
6 (heart failure adj2 (end stage or endstage or acute or decompensat* or refract*)).ti,ab,kf. (39111)
7 exp Intensive Care Units/ (229631)
8 ((intensive care adj (unit* or ward* or department* or bed*)) or ICU or ICUs).ti,ab,kf. (323840)
9 Heart Arrest/ (85318)
10 Out-of-Hospital Cardiac Arrest/ (10714)
11 (((cardiac or cardiopulmonar* or cardio pulmonar* or heart) adj2 arrest*) or asystole*).ti,ab,kf. (90813)
12 or/1-11 (760369)
13 Extracorporeal Membrane Oxygenation/ (26885)
14 ((extracorp* or extra corp*) adj2 (life support* or cardiopulmonar* resuscit* or cardio pulmonar* resuscit* or rescue* or CPR)).ti,ab,kf. (5176)
15 (((extracorporeal or extra corporeal) adj2 membrane adj2 oxygenation*) or ECMO).ti,ab,kf. (26008)
16 (cardiohelp or centrimag or rotaflow or cardiacassist or ((maquet or thoratec) adj6 (oxygenat* or extracorp* or extra corp*))).ti,ab,kf. (892)
17 (ECLS or E CLS or ECPR or E CPR).ti,ab,kf. (3518)
18 Extracorporeal Circulation/ (27374)
19 exp Cardiopulmonary Resuscitation/ (113171)
20 18 and 19 (638)
21 or/13-17,20 (38618)
22 12 and 21 (13978)
23 economics/ (248941)

24 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (787227)
25 economics.fs. (409677)
26 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (815658)
27 exp "costs and cost analysis"/ (555072)
28 (cost or costs or costing or costly).ti. (245786)
29 cost effective*.ti,ab,kf. (296887)
30 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (194906)
31 models, economic/ (11760)
32 markov chains/ or monte carlo method/ (74991)
33 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (38182)
34 (markov or markow or monte carlo).ti,ab,kf. (119420)
35 quality-adjusted life years/ (36361)
36 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (64731)
37 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (105192)
38 or/23-37 (2381363)
39 22 and 38 (580)
40 39 use medall,cctr,coch,clhta (155)
41 22 use cleed (6)
42 or/40-41 (161)
43 exp Animals/ not Humans/ (15653619)
44 42 not 43 (160)
45 limit 44 to english language [Limit not valid in CDSR; records were retained] (155)
46 cardiogenic shock/ (28422)
47 (((cardiogenic or circulatory or cardiac) adj3 shock*) or postcardiotom* or post cardiotom*).tw,kw. (33967)
48 acute heart infarction/ (66693)
49 myocarditis/ and acute.tw,kw. (8864)
50 ((acute or fulminant*) adj2 (myocardial infarct* or myocarditi* or heart attack or heart attacks)).tw,kw. (149625)
51 acute heart failure/ (17664)
52 (heart failure adj2 (end stage or endstage or acute or decompensat* or refract*)).tw,kw. (39727)
53 exp intensive care unit/ (229296)
54 ((intensive care adj (unit* or ward* or department* or bed*)) or ICU or ICUs).tw,kw. (327396)
55 heart arrest/ (85318)
56 "out of hospital cardiac arrest"/ (10714)
57 (((cardiac or cardiopulmonar* or cardio pulmonar* or heart) adj2 arrest*) or asystole*).tw,kw. (91456)
58 or/46-57 (750258)
59 extracorporeal oxygenation/ (18268)
60 extracorporeal membrane oxygenation device/ (987)
61 ((extracorp* or extra corp*) adj2 (life support* or cardiopulmonar* resuscit* or cardio pulmonar* resuscit* or rescue* or CPR)).tw,kw,dv. (5319)
62 (((extracorporeal or extra corporeal) adj2 membrane adj2 oxygenation*) or ECMO).tw,kw,dv. (26648)

63 (cardiohelp or centrimag or rotaflow or cardiacassist or ((maquet or thoratec) adj6 (oxygenat* or extracorp* or extra corp*))).tw,kw,dv. (1657)
64 (ECLS or E CLS or ECPR or E CPR).tw,kw,dv. (3596)
65 extracorporeal circulation/ (27374)
66 resuscitation/ (121845)
67 65 and 66 (712)
68 or/59-64,67 (37661)
69 58 and 68 (14103)
70 Economics/ (248941)
71 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (123452)
72 Economic Aspect/ or exp Economic Evaluation/ (433438)
73 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (840098)
74 exp "Cost"/ (555072)
75 (cost or costs or costing or costly).ti. (245786)
76 cost effective*.tw,kw. (307978)
77 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (202777)
78 Monte Carlo Method/ (60049)
79 (decision adj1 (tree* or analy* or model*)).tw,kw. (41953)
80 (markov or markow or monte carlo).tw,kw. (124385)
81 Quality-Adjusted Life Years/ (36361)
82 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (68529)
83 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (124733)
84 or/70-83 (2032934)
85 69 and 84 (577)
86 85 use emez (411)
87 (exp animal/ or nonhuman/) not exp human/ (9993792)
88 86 not 87 (409)
89 limit 88 to english language [Limit not valid in CDSR; records were retained] (404)
90 45 or 89 (559)
91 90 use medall (137)
92 90 use emez (404)
93 90 use cctr (12)
94 90 use coch (0)
95 90 use cleed (6)
96 90 use clhta (0)
97 remove duplicates from 90 (447)

Grey Literature Search

Performed: September 24–28, 2018

Websites searched:
HTA Database Canadian Repository, Alberta Health Technologies Decision Process reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), Laval University, McGill University Health Centre Health Technology Assessment Unit, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Queensland Health Technology Evaluation, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Healthcare Improvement Scotland, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, ClinicalTrials.gov, PROSPERO, EUnetHTA, Tufts Cost-Effectiveness Analysis Registry

Keywords used:
ECMO, extracorporeal membrane oxygenation, extracorporeal cardiopulmonary resuscitation, ECPR, extracorporeal life support, ECLS, cardiohelp, centrimag, rotaflow, cardiacassist, extracorporelle, oxygénation de la membrane, réanimation cardiopulmonaire extracorporelle, support de vie extracorporel

Results – Clinical (included in PRISMA): 5

Results – Economic (included in PRISMA): 6

Ongoing clinical trials (ClinicalTrials.gov): 18

Ongoing systematic reviews (PROSPERO): 11

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Systematic Reviews (ROBIS Tool)

Author, Year, Indication	Phase 2			Phase 3	
	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Study Appraisal	Synthesis and Findings	Risk of Bias in the Review
Almeida et al, 2017[25] Cardiogenic shock and cardiac arrest	High[b]	High[c]	High[d]	High[e]	High
Wang et al, 2017[24] Cardiac arrest	Low	Low	Low	Low	Low
Kim et al, 2016 Cardiac arrest	Low	Low	Low	Low	Low
Ouweneel et al, 2016[8] Cardiogenic shock and cardiac arrest	Low	Low	Low	Low	Low
Washington State Health Care Authority, 2016[26] Cardiogenic shock and cardiac arrest	Low	High[f]	Low	Low	High[23]

Abbreviations: PICO, population, intervention, comparator, outcomes; ROBIS, Risk of Bias in Systematic Reviews.
[a]Possible risk of bias levels: low, high, unclear.
[b]Potential bias due to single reviewer for title/abstract screening and full-text screening. Unclear if single reviewer used for data extraction.
[c]Potential bias due to no PICO stated and no explicit inclusion/exclusion criteria.
[d]Potential bias due to only one database searched.
[e]Potential bias due to no details regarding characteristics of studies and quality of studies not assessed.
[f]Potential bias due to no discussion regarding bias in primary studies.

Table A2: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool)

	Pre-intervention		At Intervention		Postintervention		
Author, Year	Confounding	Study Participation Selection	Classification of Interventions	Deviations from Intended Intervention	Missing Data	Measurement of Outcomes	Selection of Reported Results
Choi et al, 2016[28]	Moderate[b]	Low	Serious[c]	Low	Low	Serious[d]	Low
Mohite et al, 2018[27]	Serious[e]	Low	Serious[c]	Low	Low	Serious[d]	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk of bias levels: low, moderate, serious, critical, and no information.

[b]Confounding expected, all known important confounding domains measured (propensity score matching).

[c]Choice of intervention was solely based on surgeon's preference and experience (major aspects of the assignments of intervention status determined in a way could have been affected by knowledge of the outcome).

[d]Outcome assessors not blinded to intervention status.

[e]No methods to control for confounders.

Table A3: GRADE Evidence Profile for Comparison of Extracorporeal Cardiopulmonary Resuscitation and Traditional Cardiopulmonary Resuscitation for Adults With Cardiac Arrest

Number of Studies, Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
30-day survival							
6 observational comparative studies[a]	No serious limitations[b]	Serious limitations (−1)[c]	No serious limitations	No serious limitations	Undetected	NA	⊕ Very Low
30-day favourable neurological outcome							
5 observational comparative studies[a]	No serious limitations[b]	Serious limitations (−1)[c]	No serious limitations	No serious limitations	Undetected	NA	⊕ Very Low
Long-term survival							
5 observational comparative studies[a]	No serious limitations[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕⊕ Low
Long-term favourable neurological outcome							
5 observational comparative studies[a]	No serious limitations[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	Risk ratio > 2; lower confidence limit > 1.5	⊕⊕⊕ Moderate
Complications							
1 observational comparative study[a]	No serious limitations[b]	—	No serious limitations	No serious limitations	Undetected	NA	⊕⊕ Low
Successfully weaned or bridged to long-term ventricular assist device or heart transplant							
1 observational comparative study[a]	Serious limitations (−1)[d]	—	No serious limitations	No serious limitations	Undetected	NA	⊕ Very Low
Quality of Life							
0 studies	—	—	—	—	—	—	—
Time in intensive care							
0 studies	—	—	—	—	—	—	—
Length of stay							
1 observational comparative study[a]	Serious limitations (−1)[d]	—	No serious limitations	No serious limitations	Undetected	NA	⊕ Very Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not applicable.
[a]Observational studies start at "Low" in GRADE.
[b]Observational, mostly retrospective comparative studies; used propensity score matching to adjust for confounding variables. Patient allocation based on physician preference and location availability.
[c]Some discrepancy, particularly in results for in-hospital versus out-of-hospital cardiac arrest.
[d]Observational, mostly retrospective comparative studies; did not use propensity score matching to adjust for confounding variables. Patient allocation based on physician preference and location availability.

Table A4: GRADE Evidence Profile for Comparison of Extracorporeal Membrane Oxygenation and Standard Care for Adults With Cardiogenic Shock

Number of Studies, Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
30-day survival							
5 observational comparative studies[a]	Serious limitations (−1)[b]	Serious limitations (−1)[c]	No serious limitations	No serious limitations	Undetected	NA	⊕ Very Low
30-day favourable neurological outcome							
0 studies	—	—	—	—	—	—	—
Long-term survival							
1 observational comparative study[a]	Serious limitations (−1)[b]	—	No serious limitations	No serious limitations	Undetected	NA	⊕ Very Low
Long-term favourable neurological outcome							
0 studies	—	—	—	—	—	—	—
Complications							
2 observational comparative studies[a]	Serious limitations (−1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕ Very Low
Successfully weaned or bridged to long-term ventricular assist device or heart transplant							
3 observational comparative studies[a]	Serious limitations (−1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕ Very Low
Quality of life							
0 studies	—	—	—	—	—	—	—
Time in intensive care							
1 observational comparative study[a]	Serious limitations (−1)[b]	—	No serious limitations	Serious limitations (-1)[d]	Undetected	NA	⊕ Very Low
Length of stay							
1 observational comparative study[a]	Serious limitations (−1)[b]	—	No serious limitations	Serious limitations (-1)[d]	Undetected	NA	⊕ Very Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; NA, not applicable.
[a]Observational studies start at "Low" in GRADE.
[b]Observational, mostly retrospective comparative studies; did not use propensity score matching to adjust for confounding variables. Patient allocation based on physician preference and location availability.
[c]Discrepancy between comparators (intra-aortic balloon pump/percutaneous ventricular assist device/surgical ventricular assist device).
[d]1 study, low sample size.

Appendix 3: Selected Excluded Studies—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary Reason for Exclusion
Ahn C, Kim W, Cho Y, Choi KS, Jang BH, Lim TH. Efficacy of extracorporeal cardiopulmonary resuscitation compared to conventional cardiopulmonary resuscitation for adult cardiac arrest patients: a systematic review and meta-analysis. Scientific Reports. 2016;6:34208.	Not explicitly refractory cardiac arrest
Beyea MM, Tillmann BW, Iansavichene AE, Randhawa VK, Van Aarsen K, Nagpal AD. Neurologic outcomes after extracorporeal membrane oxygenation assisted CPR for resuscitation of out-of-hospital cardiac arrest patients: a systematic review. Resuscitation. 2018;130():146-158.	Not explicitly refractory cardiac arrest
Biancari F, Perrotti A, Dalen M, Guerrieri M, Fiore A, Reichart D, et al. Meta-analysis of the outcome after postcardiotomy venoarterial extracorporeal membrane oxygenation in adult patients. Journal of Cardiothoracic and Vascular Anesthesia 2018;32(3):1175-1182.	No comparator
Caceres M, Esmailian F, Moriguchi JD, Arabia FA, Czer LS. Mechanical circulatory support in cardiogenic shock following an acute myocardial infarction: a systematic review Journal of Cardiac Surgery 2014;29(5):743-51.	Not explicitly refractory cardiogenic shock
Cesana F, Avalli L, Garatti L, Coppo A, Righetti S, Calchera I, et al. Effects of extracorporeal cardiopulmonary resuscitation on neurological and cardiac outcome after ischaemic refractory cardiac arrest. European Heart Journal: Acute Cardiovascular Care. 2018;7(5):432-441.	Not all refractory cardiac arrest
Charon C, Allyn J, Bouchet B, Nativel F, Braunberger E, Brulliard C, et al. Ten thousand kilometre transfer of cardiogenic shock patients on venoarterial extracorporeal membrane oxygenation for emergency heart transplantation: cooperation between Reunion Island and Metropolitan France. European Heart Journal: Acute Cardiovascular Care 2018;7(4):371-378.	Wrong setting
Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, et al. Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: a meta-analysis of 1,866 adult patients. Annals of Thoracic Surgery. 2014;97(2):610-6.	No comparator
Cheng R, Hachamovitch R, Kittleson M, Patel J, Arabia F, Moriguchi J, et al. Clinical outcomes in fulminant myocarditis requiring extracorporeal membrane oxygenation: a weighted meta-analysis of 170 patients. Journal of Cardiac Failure. 2014;20(6):400-6.	No comparator
El Sibai R, Bachir R, El Sayed M. Outcomes in cardiogenic shock patients with extracorporeal membrane oxygenation use: a matched cohort study in hospitals across the United States. BioMed Research International. 2018:2428648.	No details about non-ECMO; not specifically VA ECMO; no age criteria
Ellouze O, Vuillet M, Perrot J, Grosjean S, Missaoui A, Aho S, et al. Comparable outcome of out-of-hospital cardiac arrest and in-hospital cardiac arrest treated with extracorporeal life support. Artificial Organs. 2018;42(1):15-21.	Wrong comparator
Fukuhara S, Takeda K, Kurlansky PA, Naka Y, Takayama H. Extracorporeal membrane oxygenation as a direct bridge to heart transplantation in adults. Journal of Thoracic and Cardiovascular Surgery. 2018;155(4):1607-1618.e6.	Wrong indication
Haneya A, Philipp A, Diez C, Schopka S, Bein T, Zimmermann M, et al. A 5-year experience with cardiopulmonary resuscitation using extracorporeal life support in non-postcardiotomy patients with cardiac arrest. Resuscitation. 2012;83(11):1331-7.	Letter to the editor
Hsu PS, Chen JL, Hong GJ, Tsai YT, Lin CY, Lee CY, et al. Extracorporeal membrane oxygenation for refractory cardiogenic shock after cardiac surgery: predictors of early mortality and outcome from 51 adult patients. European Journal of Cardio-Thoracic Surgery. 2010;37(2):328-33.	No comparator
Jung C, Janssen K, Kaluza M, Fuernau G, Poerner TC, Fritzenwanger M, et al. Outcome predictors in cardiopulmonary resuscitation facilitated by extracorporeal membrane oxygenation. Clinical Research in Cardiology. 2016;105(3):196-205.	No comparator
Shin TG, Choi JH, Jo IJ, Sim MS, Song HG, Jeong YK.; et al. Extracorporeal cardiopulmonary resuscitation in patients with inhospital cardiac arrest: a comparison with conventional cardiopulmonary resuscitation. Critical Care Medicine. 2011;39(1):1-7.	Superseded by more recent study
Xie A, Phan K, Tsai YC, Yan TD, Forrest P. Venoarterial extracorporeal membrane oxygenation for cardiogenic shock and cardiac arrest: a meta-analysis. Journal of Cardiothoracic and Vascular Anesthesia. 2015;29(3):637-45.	No comparator

Appendix 4: Characteristics of Included Studies—Clinical Evidence

Table A5: Observational Studies Included in the Meta-analysis by Ouweneel et al[8] Comparing Extracorporeal Cardiopulmonary Resuscitation With Conventional Cardiopulmonary Resuscitation in Adults With Cardiac Arrest

Author, Year, Country	Study type	Patient Population	Criteria for ECPR	Comparator	Follow-Up Duration	Number of Patients
Blumenstein et al, 2015[38] Germany	Retrospective Single centre	Witnessed in-hospital cardiac arrest	ECPR considered by team if CPR > 10 min and depending on cardiac etiology	Conventional CPR	"Long term" (not defined; median long-term follow-up was 1,136 days (range 823–1,415)	353
Chen et al, 2008[30] Taiwan	Prospective Single centre	Witnessed in-hospital cardiac arrest of cardiac origin; CPR > 10 min	Decision made by attending physician in charge	Conventional CPR	1 year	172
Chou et al, 2014[31] Taiwan	Retrospective Single centre	In-hospital cardiac arrest due to acute myocardial infarction; CPR > 10 min	Decision made by the cardiovascular surgeon	Conventional CPR	1 year	66
Kim et al, 2014[32] Korea	Prospective Single centre	Cardiac arrest patients with CPR (no trauma)	ECPR considered when presumed correctable cause of cardiac arrest; witnessed arrest or presumed short no-flow time when unwitnessed arrest; informed consent of the family; in-hospital CPR > 10 min	Conventional CPR	3 months	499
Lee et al, 2015[33] Korea	Retrospective Single centre	In-hospital cardiac arrest and out-of-hospital cardiac arrest	Judgment of ECMO team. ECPR used if CPR > 10 min or repetitive arrest events without return of spontaneous circulation > 20 min. No ECPR if unwitnessed out-of-hospital cardiac arrest or no bystander CPR	Conventional CPR	In hospital	955
Maekawa et al, 2013[34] Japan	Prospective Single centre	Witnessed out-of-hospital cardiac arrest of presumed cardiac origin; CPR > 20 min	Decision dependent on attending physicians	Conventional CPR	3 months	162

Author, Year, Country	Study type	Patient Population	Criteria for ECPR	Comparator	Follow-Up Duration	Number of Patients
Sakamoto et al, 2014[35] Japan	Prospective Multicentre	Out-of-hospital cardiac arrest based on ventricular fibrillation/tachycardia, no return of spontaneous circulation > 15 min after hospital arrival, < 45 min between emergency call and hospital arrival; cardiac origin	Assignment of facility to ECPR or CPR group	Conventional CPR	6 months	454
Shin et al, 2013[36] Korea	Retrospective Single centre	In-hospital cardiac arrest, witnessed, CPR > 10 min	Decision based on the discretion of the CPR team leader	Conventional CPR	2 years	406
Siao et al, 2015[37] Taiwan	Retrospective Single centre	Cardiac arrest with initial ventricular fibrillation (start CPR < 5 min), no return of spontaneous circulation after 10 min CPR	Judgment of the attending physician	Conventional CPR	1 year	60

Abbreviations: CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation.

Table A6: Observational Studies Included in the Meta-analysis by Ouweneel et al[8] Comparing Extracorporeal Membrane Oxygenation With Intra-aortic Balloon Pump or Impella/TandemHeart in Adults With Cardiogenic Shock

Author, Year, Country	Study Type	Patient Population	Criteria for ECMO	Comparator	Follow-Up Duration	Number of Patients
Chamogeorgakis et al, 2013[42] United States	Retrospective Single centre	Post infarction or decompensated cardiomyopathy (ischemic or nonischemic) cardiogenic shock	For patients receiving heart compressions, ECMO was only option. For more stable patients, TandemHeart or Impella. For isolated right ventricular failure, TandemHeart was favoured; in left ventricular failure, Impella 5.0 or TandemHeart were used	Impella 5.0/ TandemHeart	In hospital	79
Lamarche et al, 2011[44] Canada	Retrospective Single centre	Acute refractory cardiogenic shock with potential for recovery and systemic perfusion did not improve with intra-aortic balloon pump and inotropes	ECMO used for biventricular failure and oxygenation problems. Impella used for unilateral failure	Impella 5.0/ Impella RD	30 days	61
Sattler et al, 2014[40] Germany	Retrospective Single centre	Progressive cardiogenic shock due to acute myocardial ischemia and successful percutaneous coronary intervention	ECMO used if patient enrollment was during the period when ECMO was available and technically feasible	Intra-aortic balloon pump	30 days	24
Sheu et al, 2010[41] Taiwan	Prospective Single centre	ST-segment elevated myocardial infarction with primary percutaneous coronary intervention and profound cardiogenic shock (systolic blood pressure < 75 mmHg despite inotropic agents and intra-aortic balloon pump	ECMO used if patient enrollment was during the period when ECMO was available	Intra-aortic balloon pump	30 days	71

Abbreviation: ECMO, extracorporeal membrane oxygenation.

Table A7: Characteristics of Included Studies Published After the Systematic Review by Ouweneel et al[8]

Author, Year, Country	Study Type	Patient Population	Criteria for ECMO/ECPR	Comparator	Follow-Up Duration	Number of Patients
Choi et al, 2016[28] Korea	Retrospective Multicentre	Out-of-hospital cardiac arrest	Decision of ECPR implementation depended on the discretion of the attending physicians. The indications for ECPR differed depending on each hospital.	Traditional CPR	Discharge from hospital	640
Mohite et al. 2018[27] United Kingdom	Retrospective Single centre	Postcardiotomy cardiogenic shock	The choice ECMO implantation in the setting of biventricular failure particularly in cases without respiratory failure was based on the surgeon's preference and experience.	VAD	2,800 days	56

Abbreviations: ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; VAD, ventricular assist device.

Appendix 5: Additional Figures—Clinical Evidence Review

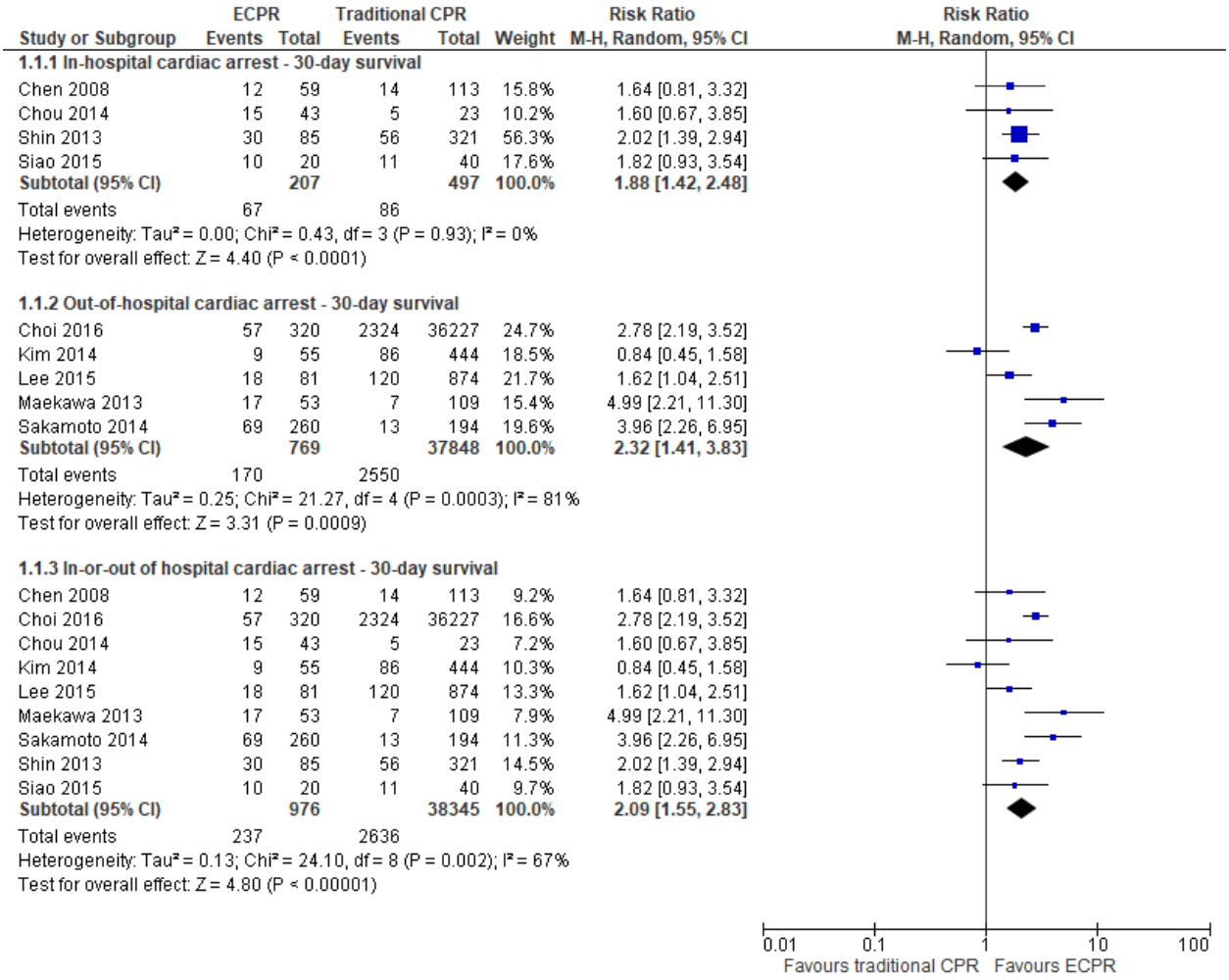

Figure A1: 30-Day Survival in Adults With Cardiac Arrest

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; M-H, Mantel-Haenszel.

Sources: Studies identified from the systematic review by Ouweneel et al, 2016,[8] and our primary literature search: Choi et al, 2016[28]; Chou et al, 2014[31]; Kim et al, 2014[32]; Lee et al, 2015[33]; Maekawa et al, 2013[34]; Sakamoto et al, 2014[35]; Shin et al, 2013[36]; Siao et al, 2015.[37]

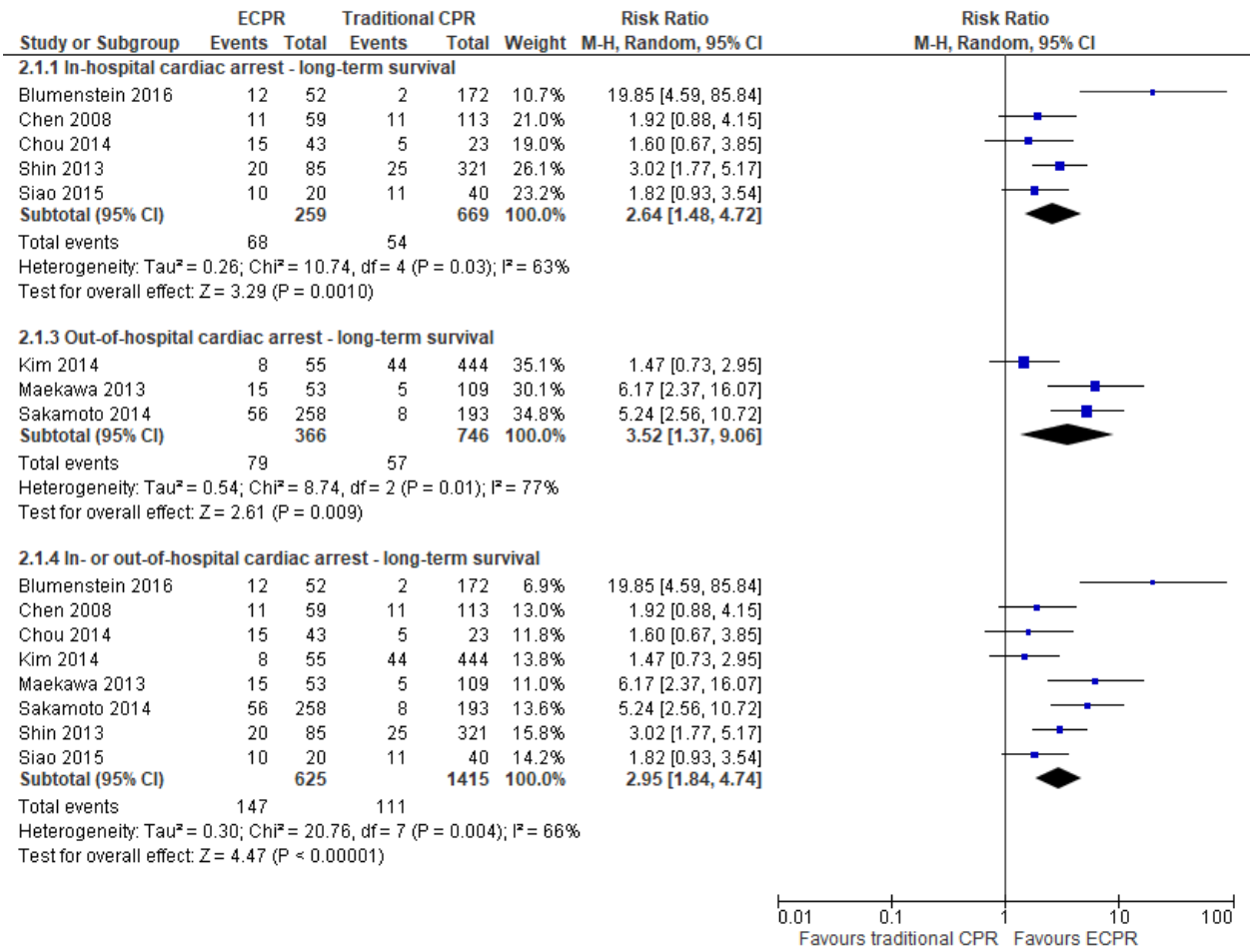

Figure A2: Long-Term Survival in Adults With Cardiac Arrest

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; M-H, Mantel-Haenszel.

Sources: Studies identified from the systematic review by Ouweneel et al, 2016,[8] and our primary literature search: Blumenstein et al, 2016[38]; Chen et al, 2008[30]; Chou et al, 2014[31]; Kim et al, 2014[32]; Maekawa et al, 2013[34]; Sakamoto et al, 2014[35]; Shin et al, 2013[36]; Siao et al, 2015.[37]

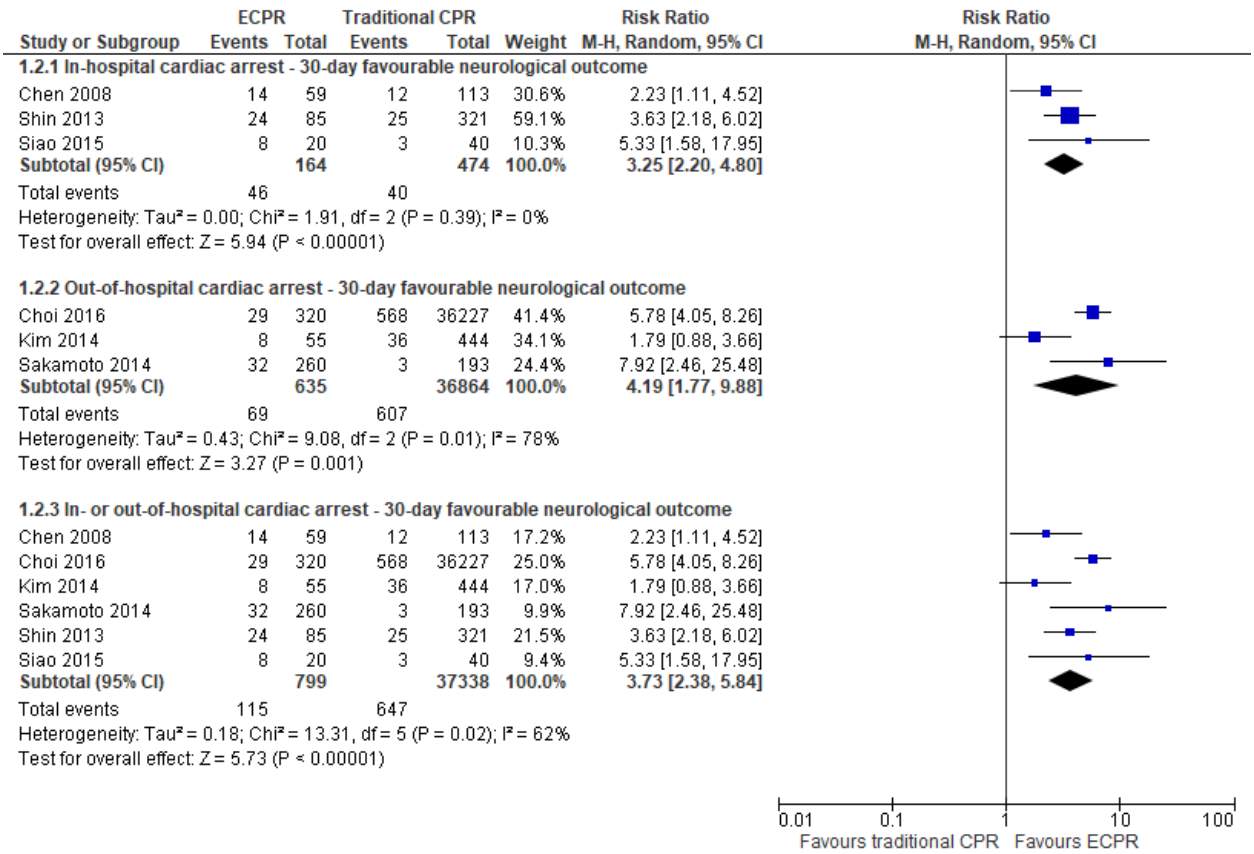

Figure A3: 30-Day Favourable Neurological Outcome in Adults With Cardiac Arrest

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; M-H, Mantel-Haenszel.

Sources: Studies identified from the systematic review by Ouweneel et al, 2016,[8] and our primary literature search: Chen et al, 2008[30]; Choi et al, 2016[28]; Kim et al, 2014[32]; Sakamoto et al, 2014[35]; Shin et al, 2013[36]; Siao et al, 2015.[37]

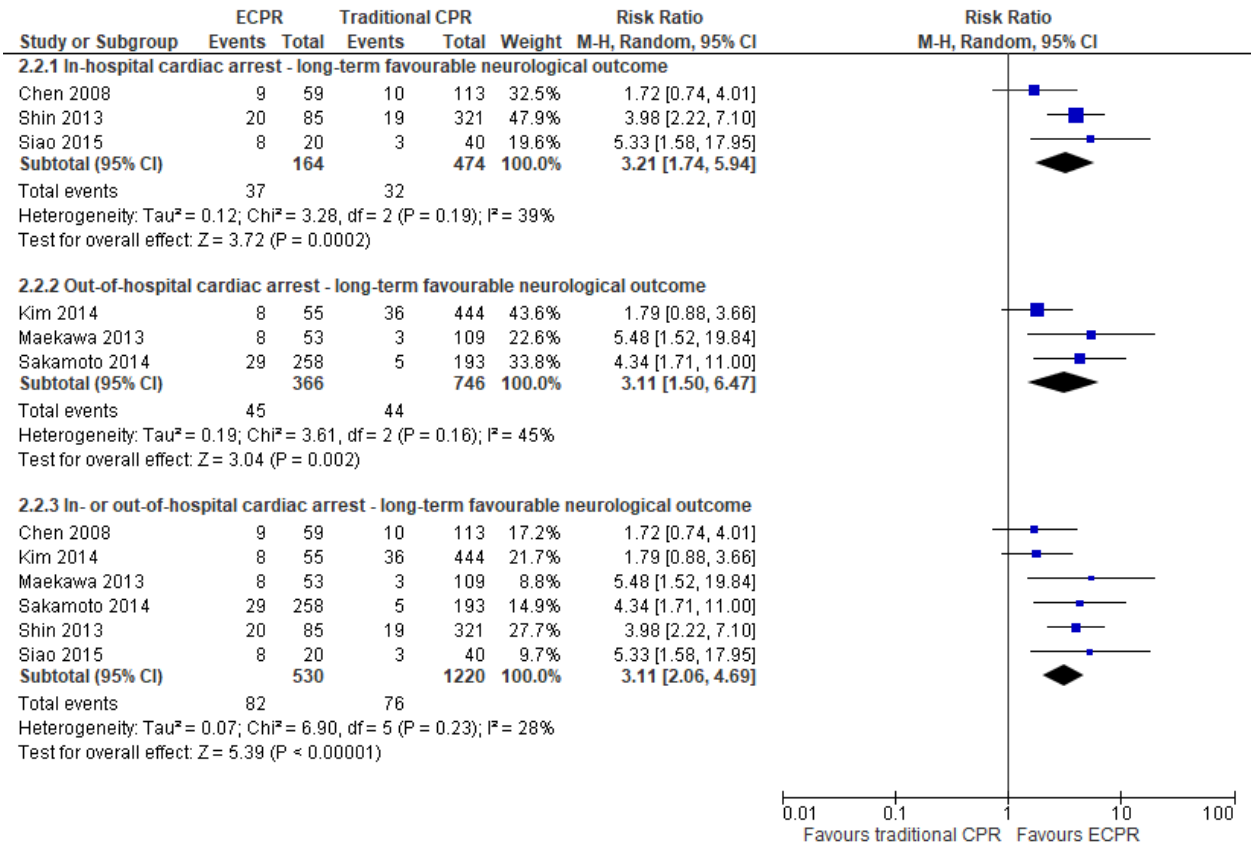

Figure A4: Long-Term Favourable Neurological Outcome in Adults With Cardiac Arrest

Abbreviations: CI, confidence interval; CPR, cardiopulmonary resuscitation; ECPR, extracorporeal cardiopulmonary resuscitation; M-H, Mantel-Haenszel.

Sources: Studies identified from the systematic review by Ouweneel et al, 2016,[8] and our primary literature search: Chen et al, 2008[30]; Kim et al, 2014[32]; Maekawa et al, 2013[34]; Sakamoto et al, 2014[35]; Shin et al, 2013[36]; Siao et al, 2015.[37]

Appendix 6: Ongoing Studies

We are aware of the following ongoing studies that have potential relevance to this review.

On ClinicalTrials.gov, we identified 18 ongoing clinical trials:

- NCT02832752 The BC Extracorporeal Cardiopulmonary Resuscitation Trial for Refractory Out-of-Hospital Cardiac Arrest
- NCT02527031 A Comparative Study Between a Pre-hospital and an In-hospital Circulatory Support Strategy (ECMO) in Refractory Cardiac Arrest
- NCT00314847 National Multicenter Randomized Trial, Comparing Two Treatments of Myocardial Infarction Complicated With Cardiogenic Shock: Standard Treatment vs. Standard Treatment Plus ECLS (Extracorporeal Life Support) (The study was stopped prematurely due to insufficient recruitment)
- NCT03528291 Decision Relevance of Transient Circulatory Support for Acute Cardiogenic Shock: Patients' Characteristics and Follow-Up
- NCT03101787 Early Initiation of Extracorporeal Life Support in Refractory OHCA (INCEPTION)
- NCT03658759 ECPR Treatment Protocol: Rapid Response VA-ECMO in Refractory Out-of-hospital Cardiac Arrest (RESuSCITATe Registry)
- NCT02754193 Effects of Induced Moderate Hypothermia on Mortality in Cardiogenic Shock Patients Rescued by Veno-arterial ExtraCorporeal Membrane Oxygenation (ECMO)
- NCT03065647 Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest (EROCA)
- NCT03637205 Prospective Randomized Multicenter Study Comparing Extracorporeal Life Support Plus Optimal Medical Care Versus Optimal Medical Care Alone in Patients With Acute Myocardial Infarction Complicated by Cardiogenic Shock Undergoing Revascularization
- NCT03327493 Impact of Adrenoreceptor Expressions on Inflammatory Pattern in Refractory Cardiogenic Shock Patients Treated by Veno-arterial Extra-Corporeal Membrane Oxygenation
- NCT03592810 Multi-center Observational Study to Assess Optimal ECMO Settings During the First Hours of Extracorporeal Cardiopulmonary Resuscitation
- NCT03508505 Postcardiotomy Venoarterial Extracorporeal Membrane Oxygenation
- NCT03261232 Prognostic Factors in Refractory Cardiac Arrest Treated With Extracorporeal Life Support at Dijon CHU
- NCT03431467 A Prospective Randomised Trial of Early LV Venting Using Impella CP for Recovery in Patients With Cardiogenic Shock Managed With VA ECMO
- NCT01298050 Refractory In and Out of Hospital Cardiac Arrest Treated With Extracorporeal Membrane Oxygenation. Observational, Single Centre, Prospective Study.

- NCT00425685 Use of Extracorporeal Membrane Oxygenation in Treatment of Acute Myocardial Infarction Following Cardiac Surgery Procedures
- NCT03323268 Validation of End-tidal CO2 for Transplumonary Blood Flow Monitoring During PVA-ECMO
- NCT03583970 Veno-arterial Extracorporeal Membrane Oxygenation Support Prior to Left Ventricular Assist Device Implantation: Initial Patients Characteristics and 6-Month Follow-up, a Retrospective Study (2013–2017) (LVAD-ECMO)

On PROSPERO, we identified 11 ongoing systematic reviews:

- Genglong Liu. The clinical efficacy of extracorporeal resuscitation for cardiac arrest in adults: a meta-analysis with trial sequential analysis. CRD42018100513
- Lars W. Andersen, et al. Extracorporeal cardiopulmonary resuscitation (ECPR) versus manual or mechanical cardiopulmonary resuscitation (CPR) for cardiac arrest: a systematic review. CRD42018085404
- Junhong Wang, et al. Predictors for discharge and neurological outcome of adults undergoing extracorporeal cardiopulmonary resuscitation: a systematic review and meta-analysis. CRD42018086774
- Guenter Klappacher, Viktoria Gruber. Systematic review of serum lactate as prognosticator in cardiogenic shock or arrest on extracorporeal membrane oxygenation (ECMO). CRD42018103570
- Sonia D'Arrigoet al. Predictors of favourable outcome after in-hospital refractory cardiac arrest treated with extracorporeal cardiopulmonary resuscitation: a systematic review and meta-analysis. CRD42017058862
- Fausto Biancari, et al. Meta-analysis of the outcome after postcardiotomy venoarterial extracorporeal membrane oxygenation in adult patients. CRD42016048140
- Renata Linertová, et al. Extracorporeal membrane oxygenation (ECMO) in patients with advanced heart failure or cardiogenic shock. CRD42016037421
- Jose Labarere, Guillaume Debaty. Prognostic factors for extracorporeal life support after out-of-hospital cardiac arrest: a systematic review with meta-analysis. CRD42016048672
- Michael Beyea, et al. Neurologic outcomes after extracorporeal membrane oxygenation assisted CPR for resuscitation of out-of-hospital cardiac arrest patients: a systematic review. CRD42015017377
- Hyun Kang, et al. Effect of extracorporeal cardiopulmonary resuscitation (ECPR): a systematic review and meta-analysis. CRD42014010547
- Ivan Ortega-Deballon, et al. Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: a systematic review of international practices and outcomes. CRD42014015259

Appendix 7: Results of Applicability Checklists for Studies Included in the Economic Literature Review

Table A8: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Extracorporeal Membrane Oxygenation for Cardiac Indications

Author, Year, Country of Publication	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Nance and Sistino, 2006,[46] United States	Partially	No	No	Yes; hospital	No	NA	No	No	Partially applicable
Roos et al, 2013,[47] Germany	Partially	Yes	No	Yes; state health insurance payer	Yes	Yes; 3.5%	Yes	Partially	Partially applicable
Maini et al, 2014,[48] United States	Partially	Yes	No	Yes; private insurer payer	Partially	Unclear	No	Partially	Partially applicable
St-Onge et al, 2015,[49] Canada	Partially	Partially	Yes	Yes; societal	Yes	Unclear	No	Yes	Partially applicable
Chang et al, 2017,[50] Taiwan	Partially	Partially	No	Yes; national insurance	Partially	Yes; 3%	Yes	Partially	Partially applicable

Abbreviation: NA, not applicable.

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).

[a]Overall judgment may be “directly applicable,” “partially applicable,” or “not applicable.”

Appendix 8: Additional Table—Budget Impact Analysis

Table A9: Predicted Yearly Number of Cardiogenic Shock Patients Receiving Extracorporeal Membrane Oxygenation or Standard Care in Ontario, Among Eligible Patients—Three-Year and Five-Year Aggressive Uptake

				New Scenario			
		Current Scenario		3-Year Implementation		5-Year Implementation	
Year	Total Eligible for ECMO	ECMO, n (Uptake)	Standard Care, n	ECMO, n (Uptake)	Standard Care, n	ECMO, n (Uptake)	Standard Care, n
2019	131	42 (32.1%)	89	69 (52.7%)	62	58 (44.3%)	73
2020	132	42 (31.8%)	90	96 (72.7%)	36	74 (56.1%)	58
2021	135	43 (31.9%)	92	126 (93.3%)	9	93 (68.9%)	42
2022	137	43 (31.4%)	94	128 (93.4%)	9	111 (81.0%)	26
2023	138	44 (31.9%)	94	129 (93.5%)	9	129 (93.5%)	9

Abbreviation: ECMO, extracorporeal membrane oxygenation.

Appendix 9: Letter of Information[a]

Ontario
Health Quality Ontario

LETTER OF INFORMATION

Health Quality Ontario is conducting a review of **Extracorporeal Membrane Oxygenation (ECMO)** for the treatment of cardiogenic shock and cardiac arrest**.** The purpose is to understand whether this device should be more broadly funded in Ontario.

An important part of this review involves speaking to patients and families of those who have experience with ECMO. Our goal is to make sure the experiences of patients and caregivers are considered in the funding recommendations for using the ECMO device.

WHAT DO YOU NEED FROM ME?

- ✓ 20-40 minutes of your time for a phone or in-person interview to share your story
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Health Quality Ontario staff. The interview will likely last 20-40 minutes. It will be held in a private location or over the telephone. With your consent, the interview will be audio-recorded. The interviewer will ask you questions about you or your loved one's condition and your perspectives about ECMO and treatment options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information collected for the review will be kept confidential and privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from your interview will be stored securely.

RISKS TO PARTICIPATION:

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their lived experience. If this is the case, please speak to our staff.

If you are interested in participating, please contact Health Quality Ontario staff:

[a] Health Quality Ontario is now the Quality business unit at Ontario Health.

Appendix 10: Interview Guide[b]

Ontario
Health Quality Ontario

Interview Questions for ECMO

Intro
Explain Health Quality Ontario purpose, health technology assessment process, and purpose of interview

Lived Experience
Background of condition or circumstances leading up to ECMO
Day-to-day routine with heart/lung health condition (if applicable)
What is the impact on quality of life?
Impact on family/caregivers, work? (if applicable)

Therapies
Were there escalating therapies attempted before ECMO (example – drugs (inotropes), intra-aortic balloon-pumps, a ventricular support device or ventricular assist device [VAD])

ECMO
Previous information surrounding these devices? (i.e., before needing it, had you ever heard of it before?)
Decision-making for treatment. Was it difficult to weigh potential risks/benefits?
Involvement in decision-making; was it patient/family/doctor decision?
Experiences with ECMO
Experiences with ECMO (from family perspective) (if applicable)
Results, impact, change in quality of life
After removed from ECMO device, do you need any further treatment? Any maintenance costs? Drawback or limitations?
Barriers to using ECMO?

[b] Health Quality Ontario is now the Quality business unit at Ontario Health.

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About Us

This health technology assessment was produced by the Quality business unit at Ontario Health, the government agency that when fully established will be responsible for ensuring all Ontarians receive high-quality health care where and when they need it.

For more information about Ontario Health, visit ontariohealth.ca.

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