TITLE

Efficacy of mechanical circulatory support devices in persons with acute cardiogenic shock or refractory cardiac arrest: Protocol for a living overview of systematic reviews

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INTRODUCTION

Acute cardiogenic shock (CS) is a state of inadequate organ perfusion due to failure of the heart pumping mechanism. CS is caused by severe impairment of myocardial performance that results in diminished cardiac output, end-organ hypoperfusion, and hypoxia. [1] Clinically this presents as hypotension refractory to volume resuscitation with features of end-organ hypoperfusion requiring pharmacological or mechanical intervention. [1] It happens in about 3.5% of patients presenting with acute heart failure and 6.6% of patients presenting with myocardial infarction. [2]. Despite advances in treatment mainly by early revascularization with subsequent mortality reduction, CS remains the leading cause of death in AMI with mortality rates still approaching 40–50% according to recent registries and randomized trials. [3,4]

Mechanical circulatory support (MCS) devices provide hemodynamic support and maintain vital organ perfusion thus providing therapeutic options for patients with CS when pharmacologic treatment is not sufficient or not suitable. While durable devices such as left ventricular assist devices (VAD) and total artificial heart are used selectively, percutaneous short-term devices, such as Impella and veno-arterial extracorporeal membrane oxygenation (VA-ECMO) are rapidly expanding and commonly used for short term mechanical support as a bridge to recovery, or as a bridge to cardiac transplant or to definitive VAD. [1,5]

Another potential use of the MCS is the cardiac arrest (CA). CA is defined as the cessation of cardiac mechanical activity and circulation, which can be confirmed by the absence of a detectable pulse, unresponsiveness, and absence of normal breathing pattern. It has been estimated that each year approximately 356,500 people suffer from out-of-hospital cardiac arrest (OHCA), and 209,000 from in-hospital cardiac arrest (IHCA) in USA. [6]. ECMO is one of the mechanical devices that has been increasingly utilized for organ and circulatory support during refractory IHCA and OHCA. [7] MCS may ensure life-saving organ perfusion, lending clinicians crucial time to identify and treat the underlying cause of cardiac arrest.

Knowledge of best current evidence will guide patient management and service planning in the hospital setting.

OBJECTIVE

To synthesise the existing evidence regarding the effectiveness and safety of mechanical circulatory support devices (Impella or ECMO) in persons with acute cardiogenic shock or refractory cardiac arrest, compared with best current intensive care treatment following clinical practice guidelines.

We plan a living overview to regularly update the available evidence.

METHODS

We plan a living overview to regularly update the available evidence.

Eligibility criteria

Types of studies

We will include:

a) Systematic reviews summarising randomised controlled trials, with or without meta-analysis, that examine the effectivity and security of MCS for CS or refractory cardiac arrest. We will define systematic reviews in accordance with definition by the Cochrane Collaboration and the PRISMA Statement: “A systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing reliable findings from which conclusions can be drawn and decisions made”. An eligible review needs to fulfill all of the following operational criteria: i) Reports searching in at least one electronic database; ii) Reports at least one criterion for the inclusion of studies We will exclude non-systematic reviews, overviews, clinical practice guidelines and primary research.

b) Randomised controlled trials (RCTs) that examine the effectivity and security of MCS for CS or refractory cardiac arrest.

Types of participants

We will consider studies that include adults (18 years old or older) with acute cardiogenic shock of any cause or with refractory cardiac arrest.

Types of interventions

For the intervention arm, we will consider studies that include MCS (Impella or ECMO), either monotherapy or in combination. For the comparison arm, we will consider best current intensive care treatment following clinical practice guidelines, including IABP and inotropic support. We will exclude cross-over trials.

Types of outcomes

We will consider a study eligible if it includes any of the following outcomes:

- Main outcomes: Mortality of cardiovascular cause, Mortality of any cause, Adverse events derived from the device, Quality of life measured by validated questionnaires
- Additional outcomes: Costs

Search methods for identification of studies

Our literature search was devised by the team maintaining the L·OVE platform (https://app.iloveevidence.com), using the following approach:

1. Identification of terms relevant to the population and intervention components of the search strategy, using Word2vec technology[9] to the corpus of documents available in Epistemonikos Database.
2. Discussion of terms with content and methods experts to identify relevant, irrelevant and missing terms.
3. Creation of a sensitive boolean strategy encompassing all the relevant terms

Our main search source will be Epistemonikos database (https://www.epistemonikos.org), a comprehensive database of systematic reviews and other types of evidence, maintained by screening multiple information sources to identify systematic reviews and their included primary studies, including Cochrane Database of Systematic Reviews, Pubmed/MEDLINE, EMBASE, CINAHL, PsycINFO, LILACS, DARE, HTA Database, Campbell database, JBI Database of Systematic Reviews and Implementation Reports, EPPI-Centre Evidence Library[10]. An additional search will be performed on PubMed in order to identify randomized trials/primary studies not included in reviews.

The searches will cover from the inception date of each database. No publication status or language restriction will be applied to the searches in Epistemonikos or the additional searches.

We will keep a living search in the L·OVE platform every three months for a period of 12 months to detect new SRs or RCTs that could potentially be included in our overview. The monitoring will start three months from the date of first literature search. The detailed search strategy is shown in Annex 1. We will also perform searches in clinicaltrials.gov, the International Clinical Trials Registry Platform, PROSPERO and looking the reference list of all included reviews every six months.

Selection of studies
The selection and allocation will be conducted in several steps:

First, the results of the literature search in the repository will be automatically incorporated into the L·OVE platform (automated retrieval), where the titles and abstracts will be independently screened by at least two reviewers against the inclusion criteria. Secondly, we will obtain the full reports for all records that appear to meet the inclusion criteria or require further analysis to decide about their inclusion. Finally, we will validate these classifications and include reviews that assessed comparisons between Impella or ECMO and conventional treatments regarding guidelines in patients with cardiogenic shock or cardiac arrest. Two authors independently will evaluate reviews for suitability for inclusion and any disagreement will be resolved by consensus between all authors.

We will record the reasons for excluding SRs in any stage of the search and outline the study selection process in a PRISMA flow diagram adapted for the purpose of this project.

Data extraction
Data regarding participant characteristics, number of included trials, date of last search update, intervention and comparisons, outcomes, and results of each review will be independently extracted by two authors and compared a posteriori. Any disagreement will be resolved by consensus between all authors. We will use an online Excel form to collect data.

Assessment of methodological quality and risk of bias of included studies
Two authors will independently assess the quality of each SR using the AMSTAR-2 tool. We will resolve discrepancies in the ratings by consensus of two authors, and if necessary, by a third reviewer. We will report the risk of bias of primary studies undertaken by the authors of

each SR. We will not assess primary studies. If more than one SR includes the same primary study, we will collect data from the SR that had the best quality based on AMSTAR-2 results.

We will assess the quality of additional RCT identified in the living search by using the GRADE approach[11].

Data synthesis and analysis

We will perform the novo meta-analyses for each comparison based on the data of each primary study extracted from included SRs. We will assess the heterogeneity of included studies with I2. If there is very high heterogeneity (>= 90%) we will not perform a meta-analysis and will only describe the results of the included SRs in a narrative and tabular way.

We will explore subgroup analysis according to the ethiology of acute cardiogenic shock, type of MCS (Impella or ECMO), history of previous cardiopulmonary arrest, sex and age.

We will assess the presence of possible publication bias by using a funnel plot.

Assessment of certainty of the evidence

We will assess the certainty of the evidence according to GRADE guidance11 and create a Summary of Findings table for the main outcomes (mortality of cardiovascular cause, mortality of any cause, adverse events, and quality of life).

Evidence monitoring and surveillance plan

In order to maintain the living evidence process for this review, the Epistemonikos-L.OVE platform (10) will be used as technological enable to support the evidence identification, screening, and selection. We will keep a living search in the L·OVE platform to detect systematic reviews and randomized controlled trials. Additionally, each three months, we will manually search for ongoing studies in the WHO International Clinical Trials Registry Platform and the clinicaltrials.gov.

One reviewer will be in charge of assessing the evidence that has entered the L.OVE of this question every month and apply the selection criteria presented above. If a potentially eligible study is found, a second reviewer will confirm its eligibility by reading the full text. Results of evidence surveillance will be collected and keep as part of the study records. Information on PRISMA will be updated accordingly. Criteria for selecting studies will be revised and changed accordingly during the LE processes each 4 months.

All new eligible studies will undergo to data extraction process. The data synthesis will be update immediately after that taking into account the predefined subgroups of interest, and the body of evidence for the outcomes of interest will be assessed following the GRADE approach accordingly looking for changes on the certainty assessment results.

The living process for this question will end after 12 months of surveillance updating the evidence synthesis report.

Statistical considerations for the living evidence synthesis

The inclusion of new studies identified as part of evidence surveillance and reporting on the outcomes of interest will follow this approach: We will perform a meta-analysis for each of the outcomes of interest reported by the new studies using a fixed-effect model in order to evaluate the statistical heterogeneity among included studies by using the I2 statistics. If new heterogeneity is detected (i.e. increase the heterogeneity previously identified or new heterogeneity arises where it was previously undetected), we will explore its potential sources by reviewing the new studies against previously included studies in order to identify reasons that may explain inconsistent results among studies. In presence of unexplained heterogeneity (I2> 70%), we will consider not to Meta-analyze them and explain the evidence synthesis narratively. If the I2 is below 90%, we will perform a meta-analysis by using the fixed effects of the random effects model, whichever pertinent.

Dissemination plan

We plan to communicate our review results as publication in a scientific journal.

If during the living process, new relevant results that imply changes in the current clinical practice are identified, we will update the report of this review and disseminate the update among potential users.
We will elaborate evidence technical reports to the hospital Health Assessment Committee. We will share the results through our social media channels. All periodical updates will be available in the LE_IHD project website (https://livingevidenceframework.com/en/).

We plan to disseminate our results in social media and with a publication at the end of the evidence surveillance process.

FOUNDING SOURCE
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CONFLICT OF INTEREST
None

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Annex 1. Boolean search strategy (July 2021)

Epistemonikos:

(("cardiac shock" OR "cardiogenic shock" OR "heart failure" OR "ventricular dysfunction" OR "systolic dysfunction" OR "cardiac insufficiency" OR "heart insufficiency" OR ((reduced OR decreased) AND "ejection fraction") OR ((cardiac* OR cardiopulmonar* OR cardiorespiratory* OR "cardio-pulmonary") AND (((arrest* OR resuscit* OR "life support" OR "life-support")) OR asystol* OR (ventricular* AND fibrillation*) OR vf OR cpr OR pulseless* OR "e-cpr") OR "low cardiac output" OR "acute coronary" OR "coronary syndrome" OR ((myocard* OR heart) AND infarct*) OR "acute mi" OR "st-segment" OR "st-elevation" OR nste OR nstemi OR "nste-acs" OR nsteacs OR "non-st" OR "non-st-segment" OR "non-st-elevation" OR (unstable AND (angina OR coronary)) OR ((pulmon* AND (embol* or thromboemboli*))) OR ((angina* OR ischemia) AND (attacks OR effort OR "exercise-induced" OR (exercise AND induced))))) AND ((((((ventricular* OR biventricular* OR cardiac* OR heart* OR mechanical* OR circulatory*) AND (assist* OR support*) AND (device* OR system OR mechanical*)) OR lvad* OR bivad* OR "assist device" OR "device support" OR "heart support" OR "ventricular assist" OR "heart assist") OR (iabp* OR iabc* OR (balloon* AND (pump* OR "intra-aortic" OR intraaortic* OR "intra aortic")) OR counterpulsation* OR "counter-pulsation" OR "balloon support" OR "balloon pulsation") OR (Impella* OR (abiomed* AND (assist* AND device*) OR (heart AND pump*))) OR (((venoarteri* OR arteriovenous* OR "veno-arterial") AND (ecmo OR extracorporeal* OR "extra-corporeal" OR (membrane* AND oxygenat*))) OR "va-ecmo" OR "av-ecmo" OR vaecmo* OR avecmo* OR "va ecmo" OR "av ecmo" OR "va-ecls" OR "av-ecls" OR vaecls* OR avecls* OR "va ecls" OR "av ecls")))

Medline. PUBMED:

(("cardiac shock" OR "cardiogenic shock" OR "heart failure" OR "ventricular dysfunction" OR "systolic dysfunction" OR "cardiac insufficiency" OR "heart insufficiency" OR ((reduced OR decreased) AND "ejection fraction") OR ((cardiac* OR cardiopulmonar* OR cardiorespiratory* OR "cardio-pulmonary") AND (((arrest* OR resuscit* OR "life support" OR "life-support")) OR asystol* OR (ventricular* AND fibrillation*) OR vf OR cpr OR pulseless* OR "e-cpr") OR "low cardiac output" OR "acute coronary" OR "coronary syndrome" OR ((myocard* OR heart) AND infarct*) OR "acute mi" OR "st-segment" OR "st-elevation" OR nste OR nstemi OR "nste-acs" OR nsteacs OR "non-st" OR "non-st-segment" OR "non-st-elevation" OR (unstable AND (angina OR coronary)) OR ((pulmon* AND (embol* or thromboemboli*))) OR ((angina* OR ischemia) AND (attacks OR effort OR "exercise-induced" OR (exercise AND induced))))) AND ((((((ventricular* OR biventricular* OR cardiac* OR heart* OR mechanical* OR circulatory*) AND (assist* OR support*) AND (device* OR system OR mechanical*)) OR lvad* OR bivad* OR "assist device" OR "device support" OR "heart support" OR "ventricular assist" OR "heart assist") OR (iabp* OR iabc* OR (balloon* AND (pump* OR "intra-aortic" OR intraaortic* OR "intra aortic")) OR counterpulsation* OR "counter-pulsation" OR "balloon support" OR "balloon pulsation") OR (Impella* OR (abiomed* AND (assist* AND device*) OR (heart AND pump*))) OR (((venoarteri* OR arteriovenous* OR "veno-arterial") AND (ecmo OR extracorporeal* OR "extra-corporeal" OR (membrane* AND oxygenat*))) OR "va-ecmo" OR "av-ecmo" OR vaecmo* OR avecmo* OR "va ecmo" OR "av ecmo" OR "va-ecls" OR "av-ecls" OR vaecls*

OR avecls* OR "va ecls" OR "av ecls"))) AND ((randomi* OR RCT OR placebo* OR trial OR "controlled-trial" OR randomly*)))