Clinical and cost effectiveness of left ventricular assist devices as destination therapy for advanced heart failure

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Review question

Question 1. What is the clinical effectiveness of LVAD when used for long-term treatment of advanced heart failure (destination therapy)?

Question 2. What is the cost effectiveness of LVAD when used for long-term treatment of advanced heart failure (destination therapy)?

Searches

Question 1 – Clinical Effectiveness

For clinical effectiveness, databases to search for primary studies will be Cochrane Library (CENTRAL), MEDLINE and Embase. For any relevant systematic reviews we will search Epistemonikos, the Cochrane Library of Systematic Reviews and MEDLINE and Embase. Searching will use free text and index terms related to population and intervention, with no restriction by study design. An example search strategy for MEDLINE can be seen in the appendix. The search term combinations in the example search strategy to be applied to the bibliographic databases were formulated in the standard way for a review and then augmented to ensure the strategy was sensitive to capturing studies known to the review whilst keeping the yield to manageable numbers of records.

No restriction by date or language of publication will be placed on searches. Systematic reviews found will be used to identify additional primary studies as will citation checking of included studies. Grey literature (e.g. institutional reports) will be sought from key organisations. Conference abstracts will not be excluded. We will search for ongoing and recently completed trials using the WHO portal.

We will also approach mechanical circulatory support registries (e.g. EUROMACS and INTERMACS registries) for any potentially relevant data on patients with LVADs for destination therapy. Our searches will also identify any data published from relevant registries.

Question 2 – Cost Effectiveness

For cost-effectiveness studies we will use the same approach to searching as above, whilst targeting additional databases Economic databases EconLit, Cost-Effectiveness Analysis (CEA) registry and the NHS Economic Evaluation Database (NHSEED). We note that some of these are no-longer updated, but they may still contain useful studies that would not be found elsewhere.

Types of study to be included

Question 1 -

For clinical effectiveness we will include any clinical trial whether randomised, non-randomised or single arm. We will also include all observational studies including cohort, case-controls and case series designs.

Systematic reviews will be included to identify any additional potentially relevant primary studies.

Question 2 -

For cost effectiveness we will select for review all studies that report economic evaluations (cost-consequence analysis, cost-benefit analysis, cost effectiveness analysis, cost-utility analysis) and any cost studies

Condition or domain being studied

Advanced heart failure (AHF) is characterised as a stage of heart failure whereby standard treatment is no longer effective in controlling symptoms. Patients often have deteriorating heart function, increased symptom burden, and declining physical capacity. This results in the need for advanced therapies such as cardiac transplantation and mechanical circulatory support, ending in palliative care. Cardiac transplantation is considered the leading treatment for AHF due to the resulting high survival rates versus standard medical management. However, given the increasing burden of HF and the limited availability of donor hearts, the option of transplantation is restricted to a small number of patients.

Another potential treatment option for patients with AHF is the implantation of a mechanical circulatory support device. The devices may be given to patients who are awaiting transplant (bridge to transplant), or to patients who it is believed may in the future be suitable for transplant (bridge to candidacy). For those patients who are ineligible for transplant, the LVAD is also being considered as a long-term treatment offering permanent circulatory support. This is known as destination therapy.

Participants/population

Question 1 and 2.

Patients with advanced heart failure who are receiving LVAD as destination therapy and are ineligible for transplant or potential candidacy at the time the LVAD is implanted. Studies with mixed LVAD populations will also be included where separate destination therapy data is reported or can be acquired. Eligibility for heart transplantation is defined by individual centres based on international guidelines, but there may be variations in practice.

Intervention(s), exposure(s)

Question 1 and 2.

Left ventricular assist device (LVAD). There will be no restriction placed on the type of LVAD either by mechanism or generation (e.g. first-generation pulsatile pump, second generation continuous axial flow or third generation centrifugal flow).

Comparator(s)/control

Question 1 and 2.
Optimal medical management or different generation or type of devices or no comparator

Main outcome(s)

Question 1.

Any relevant outcome will be considered.

Question 2.

Outcomes will be quality of life (QoL), cost and incremental cost-effectiveness ratios.

* Measures of effect

E.g. mean difference for continuous data/standardised mean difference when pooling from studies using different tools measuring the same outcome, relative risks for dichotomous data, hazard ratios for survival, % of patients for adverse events

Additional outcome(s)

Any relevant outcomes for example survival/mortality data, patient-related data e.g. quality of life, service utilisation including hospitalisations, length of stay data etc., device outcomes/procedural events and

classification/function measurements such as INTERMACS heart failure classification and the six minute walking test as well as any other relevant outcomes

* Measures of effect

E.g. mean difference for continuous data/standardised mean difference when pooling from studies using different tools measuring the same outcome, relative risks for dichotomous data, hazard ratios for survival, % of patients for adverse events

Data extraction (selection and coding)

For data extraction we will use a predefined, piloted data extraction form. Where possible we will contact study authors to acquire data from relevant subgroups within mixed populations, as well any missing data relating to study design, population characteristics, interventions/comparators and outcomes. Data extraction will be conducted by two independent reviewers with a third to resolve discrepancies if consensus cannot be reached.

Question 1 –

Study characteristics (author details, study design, population, inclusion criteria, length of follow-up, setting etc.)

Patient characteristics (age, sex, NYHA class, INTERMACS class, comorbidities etc.)

Intervention/comparator (type of LVAD, generation of LVAD, comparator etc.)

Outcomes (Any relevant outcomes for example survival/mortality data, patient-related data e.g. quality of life, service utilisation including hospitalisations, length of stay data etc., device outcomes/procedural events and classification/function measurements such as INTERMACS heart failure classification and the six minute walking test as well as any other relevant outcomes)

All outcomes will be extracted at all relevant time points reported in each study.

Question 2 –

Further to the relevant data above, from cost effectiveness studies we will also extract data including types of model used, range of health states utilised in any models and types of inputs used in the models for the three types of parameter representing patient transitions, resource use and quality of life measures. This will include any data reported whether or not they appear directly related to heart failure.

Risk of bias (quality) assessment

Question 1 –

For risk of bias assessment we will use tools appropriate to the study design. For randomised and non-randomised trials the Cochrane Risk of Bias tool 2 for RCTs will be used. The randomisation domain will be relaxed for non-randomised trials and we acknowledge that blinding is not possible in most surgery trials.

For single arm trials and case series, a tool based on the Joanna Briggs Checklist for Case Series will be used.

For other observational studies including cohort and case-control designs, the Newcastle-Ottawa scale will be used to assess risk of bias.

Question 2 –

The Consensus on Health Economic Criteria (CHEC) tool for economic evaluation will be used to assess the quality of cost effectiveness studies. For any model-based studies that are found the Philips checklist will be utilised

Risk of bias assessment will be conducted by two independent reviewers with a third to resolve

discrepancies if consensus cannot be reached.

Strategy for data synthesis

Question 1 –

AHF patients can be categorised on the Interagency Registry for Mechanical Circulatory Support (INTERMACS) seven step scale, with a level 1 denoting critical cardiogenic shock and level 7 ascribed to stable patients living with meaningful activity limited to mild exertion. The main analysis will stratify patients into INTERMACS scores (e.g. score 2/3 or score 4/5). Within these categories, randomised and observational studies comparing any LVAD device with any other device or medical management will be synthesised using meta-analysis and network meta-analyses (NMA) methods where appropriate. The most up-to-date methods for incorporating observational data in NMAs will be used including contacting methodology groups known to be working on this topic to identify any further methodology papers pre-publication. We will assess the transitivity assumption epidemiologically by comparing the clinical and patient characteristics of the studies to those of the contemporary target population. Within the evidence network, formal statistical assessment of evidence consistency using local and global methods will be performed where possible. We will consider trends over time in other observational data to inform sensitivity analysis about how relative effects on outcomes may have changed over time due to changes in medical management. In all parts of the analyses we will where possible look to explicitly estimate parameters to adjust for potential biases when using study data to estimate parameters relating to our target population. Central estimates and confidence intervals will be used to inform the cost-effectiveness model.

Question 2 –

We will undertake a descriptive analysis of included studies to compare and contrast approaches to economic evaluation, model structures, time horizons, cycle lengths and parameter inputs. This will include assessment of assumptions and the validity of model inputs in relation to the findings of the clinical effectiveness review above, and the sources of costs and utility values.

Analysis of subgroups or subsets

By INTERMACS score.

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Type and method of review

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SL and DQ have previously received educational grants from Abbott

DM, PB, MP, SB, DP, JD have no conflicts

Yes

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England

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Review Ongoing

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Subject indexing assigned by CRD

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Stage of review at time of this submission
The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add

publication details in due course.

Versions

20 May 2020