Clinical and cost-effectiveness of left ventricular assist devices as destination therapy for advanced heart failure: systematic review and economic evaluation

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Published August 2024
DOI: 10.3310/MLFA4009

Scientific summary

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Health Technology Assessment 2024; Vol. 28: No. 38
DOI: 10.3310/MLFA4009

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Scientific summary

Background

Heart failure is a debilitating, progressive syndrome characterised by the inability of the heart to pump blood around the body. Pharmacological treatments are used as first-line treatment but may eventually become less effective and left ventricular assist devices (LVADs) or heart transplant (HT) are considered. LVADs are frequently used as bridge to transplant (BTT) or bridge to candidacy (BTC). However, some patients are ineligible for HT and either continue on medical management (MM) or could have a LVAD implanted as 'destination therapy' (DT). LVAD as DT is not currently commissioned within the United Kingdom National Health Service (UK NHS). The costs of LVADs are high, especially when compared to the alternative MM, but may also offer significant benefit in terms of survival. It is important to determine whether LVADs are both clinically and cost-effective as DT to inform decision-making from the UK NHS/personal social service (PSS) perspective on their potential as long-term treatment for advanced heart failure patients ineligible for HT.

Aims and objectives

What is the clinical and cost-effectiveness of a LVAD compared to MM for advanced heart failure (AHF) patients ineligible for HT (DT)?

The specific objectives to address this aim were to undertake:

- a systematic review of available evidence on the clinical effectiveness of a LVAD as DT, including a network meta-analysis (NMA) to provide an indirect estimate of the relative effectiveness of currently available LVADs compared to MM;
- a systematic review of available economic evidence on the use of a LVAD as DT; and
- the development of an economic model to estimate the cost-effectiveness of a LVAD compared to MM from the UK NHS/PSS perspective.

Due to the withdrawal of the HeartWare ventricular assist device (HVAD) during the undertaking of this research, the analyses primarily focus on the HeartMate 3™ (Abbott, Chicago, IL, USA) device, the only LVAD available in the UK at this time.

Methods

Systematic review of clinical effectiveness

A systematic review was undertaken of all LVADs as DT and reporting followed the general principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The review was registered on PROSPERO (CRD42020158987).

Eligibility criteria

Studies of patients over 16 years of age with AHF who received any type of LVAD as DT were included. The review considered all devices, but the analysis focused on the HM3 device due to the recent withdrawal of the HeartWare HVAD (Medtronic, Dublin, Republic of Ireland). Eligible comparators (where relevant) were MM and other LVADs. Outcomes were survival, quality of life (QoL), hospitalisations, major events, complications and functional status.

Study designs eligible were any clinical trial (whether randomised, non-randomised or single arm), observational studies (cohort, case-controls and case series) and reports from patient registries [e.g. INTERMACS, International Registry for Mechanically Assisted Circulation (IMACS)]. Studies were eligible if 50 or more DT patients were included. Systematic reviews were included and used to identify any additional potentially relevant primary studies.

Searches and study selection

Databases were searched from inception to 20 May 2020, with an updated search on 11 January 2022. Databases searched included Cochrane Library (CENTRAL), MEDLINE and EMBASE via Ovid, Epistemonikos, Cochrane Library of Systematic Reviews and World Health Organization (WHO) clinical trials portal (for ongoing studies). There were no restrictions by language or date of publication.

Two reviewers independently undertook title and abstract screening and full-text selection via Covidence (Veritas Health Innovation, Melbourne, VIC, Australia). Disagreements were resolved by a third reviewer or consensus and reasons for exclusion were recorded.

Risk of bias, data extraction and synthesis

Quality assessment and data extraction were completed by one reviewer and checked by a second. Appropriate risk-of-bias tools dependent upon study design were applied.

A hierarchical approach to synthesis was undertaken to avoid double-counting of studies with overlapping patient data and to manage the large volume of evidence. Randomised controlled trials (RCTs) and controlled non-randomised trials were considered in the first instance. Registry reports and uncontrolled observational studies were used to supplement findings for all outcomes. Data were tabulated and analysed in a narrative approach by device, and forest plots without summary estimates were presented (and where appropriate the feasibility of meta-analysis was considered).

A network meta-analysis was considered for the main outcomes to produce an indirect comparison of the HM3 device (across LVAD generations) to MM, but only carried out for survival.

Systematic review of cost-effectiveness

A systematic review of the cost-effectiveness of LVADs was carried out utilising the same search strategy, and at the same time as the clinical effectiveness review, with the addition of three further specialist economics database searches in EconLit, Cost-Effectiveness Analysis (CEA) registry and the NHS Economic Evaluation Database (NHS EED). Appropriate risk-of-bias tools were applied and a narrative synthesis was undertaken.

Economic evaluation

The systematic reviews' findings were used to inform the development of a cost–utility analysis (CUA), from the NHS/PSS perspective, using a Markov model with a lifetime horizon and 1-month cycles. Along with evidence from the reviews, the model was informed by guidance from clinical specialists, patients and commissioners. All costs used were in 2019 prices, and a discount rate of 3.5% was applied as per the national UK guidelines. To produce the base case, mortality risks for MM and LVAD arms required some assumptions and several methods for estimating the risks were identified. Two of these were primarily utilised: non-comparative net weight estimates and comparative estimates mapped to LVAD data from the recent relevant HM3 trial (MOMENTUM).

The analysis was repeated incorporating a small probability of LVAD DT recipients transitioning to HT eligibility. The potential impacts of the severity of heart failure on cost-effectiveness were explored by considering subgroupings of profiles based on the INTERMACS classification. Uncertainty was explored via both deterministic and probabilistic sensitivity analyses, paying specific attention to the life expectancy and ongoing costs.

Results

Systematic review of clinical effectiveness

There were 240 articles from 134 studies included in the clinical effectiveness review (5 randomised trials, 1 non-randomised trial, 86 observational studies, reports from 5 registries, 5 ongoing studies and 32 systematic reviews). Of the six trials that were included, only one of these assessed the HM3 and this was in comparison to the previous generation HeartMate II device (MOMENTUM RCT). The majority of HM3 data comes from this trial, with minimal additional data contributions from registry reports or observational studies of single cohorts. The MOMENTUM study was considered as having some concerns regarding risk of bias; however, this was primarily due to the per-protocol analysis for the DT participants and most other domains were considered low risk.

There were 624 DT patients in the MOMENTUM 3 trial in total, with a mean age of 63 [standard deviation (SD) 12], 82.2% male and 52.1% INTERMACS level 3.

At the longest follow-up point (24 months) survival was 76.7% in HM3 DT patients compared to 59% in HeartMate II patients. Clear and significant improvements in QoL from baseline were reported at 12 months and maintained at 24 months in the HM3 group; however, this was similar in the HeartMate II group. Major events and complications were present in both groups by the 24-month follow-up. There were eight stroke events per 100 patient-years in the HM3, as well as one pump thrombosis event and 70 bleeding events per 100 patient-years. These were all lower than that of the HeartMate II group. Rehospitalisations were also significantly lower in HM3 patients.

While some reports included HM3 patients, there were no HM3 specific data reported in any patient registry reports. One observational study reported that HM3 patients (n = 15) had 0 pump thrombosis events in 24 months of follow-up.

While it was not the focus due to withdrawal, survival levels were lower in the HeartWare HVAD trials when compared to the HM3 in the MOMENTUM trial and there were concerns with the stroke rates reported in the evidence.

Risk of bias across the included trials varied with all but two studies reporting an overall high risk of bias or with some concerns for at least one outcome.

The evidence contained within the remaining trials, observational studies and registry reports mostly relate to devices other than HM3. This evidence is summarised in the main part of this report.

Indirect comparison of HeartMate 3 and medical management

As there were no studies directly comparing HM3 and MM, indirect comparisons of the trial data were required utilising MM data from the older REMATCH trial (the first RCT comparing the first-generation HeartMate device to MM). Data were available to link through available studies for the survival outcome only. The network meta-analysis demonstrated a reduction in the risk of mortality, relative risk of death of 0.25 [95% confidence interval (CI) 0.13 to 0.47] 24 months, with the HM3 compared to MM.

Systematic review of cost-effectiveness

There were 19 studies reported in 20 articles included in the cost-effectiveness review: 5 cost analyses and 14 economic evaluations. Nine studies were US-based and four were UK-based. Most of the studies aimed to compare the health and cost outcomes of LVADs with MM. Most economic evaluations (n = 12) used a CUA approach and only two conducted a CEA. Markov-based modelling was applied in eight studies. The perspective, where stated, was the service provider in most studies. Healthcare resource use was usually estimated based on small numbers of patients from a single centre, which resulted in variability.

In the studies comparing LVAD with MM for DT patients, the incremental cost per quality-adjusted life-year (QALY) gained estimates ranged between £46,207 and £238,401 in 2019 prices over a time horizon of 5 years or longer and from different perspectives. The overall quality of the studies was considered poor to moderate. Some limitations were limited consideration of uncertainty, insufficient time horizon and lack of consideration of some key complications and cost components. Only one study looked at the impact of disease severity on cost-effectiveness. More recent evaluations tended to have lower estimates of incremental cost-effectiveness, presumably reflecting better clinical outcomes of more recent devices. Two recent studies estimated the cost-effectiveness from a UK perspective, deriving incremental cost-effectiveness ratios of £47,361 and £46,207 per QALY gained for the HeartWare device (device withdrawn in 2021) and the HM3 device, respectively compared to MM.

Economic evaluation

The economic evaluation found similar results for each base case:

- Non-comparative net weight estimates approach: LVAD would produce an additional 2.86 QALYs per person, increase life expectancy by 3.73 years and the incremental cost to the NHS would be £152,735 per person. Incremental cost-effectiveness ratio (ICER): £53,496.
- Comparative estimates mapped to LVAD in MOMENTUM approach: LVAD would produce an additional 2.51 QALYs per person, increase life expectancy by 3.06 years and the incremental cost to the NHS would be £146,275 per person. ICER: £58,244.

At a willingness to pay threshold of £50,000 per QALY gained, LVADs would not be considered cost-effective compared to MM for AHF patients ineligible for HT. The same applied when severity weighted ICER estimates based on QALY shortfall methods were used. The deterministic sensitivity analysis showed that inclusion of the probability of becoming eligible for a HT did not change these findings. Furthermore, the findings did not differ in subgroup analyses based on severity of heart failure. Model outputs were most sensitive to estimates related to outpatient costs for both LVAD and MM.

Conclusions

LVADs have significantly improved over time and the currently available HM3 LVAD is considered clinically effective in patients with end-stage heart failure ineligible for transplant, offering survival of over 75% at 2 years of follow-up with reduced complications and major events in comparison to older devices. However, the device compared to MM may not be considered cost-effective when using methods of defining this for end of life in the UK.

Future research

Currently, no RCT has been published that compares the HM3 device to MM; however, there is an ongoing trial (SweVAD) comparing the two, which is due to complete final study follow-up in December 2023. This randomised trial, undertaken in Sweden, should allow for relative effects to be determined between the two interventions. This will ultimately enable more robust data to be used to update the current model, rather than relying upon indirect comparisons with wide uncertainty.

However, further issues around the true cost of MM are still present due to the lack of recent data on these costs in the UK. An audit of MM costs in DT patients in the UK would address this.

Issues also persist in developing reliable subgroup analyses based on severity profiles to aid identification of whether a LVAD is (more) cost-effective for some groups of DT patients. Future trials and other studies should report results by patient severity profiles (e.g. INTERMACS classification), and if registry/observational studies then also by device implanted.

Study registration

This study is registered as PROSPERO CRD42020158987.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment programme (NIHR award ref: NIHR128996) and is published in full in *Health Technology Assessment*; Vol. 28, No. 38. See the NIHR Funding and Awards website for further award information.

Health Technology Assessment

ISSN 2046-4924 (Online)

Impact factor: 3.6

A list of Journals Library editors can be found on the NIHR Journals Library website

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This article

The research reported in this issue of the journal was funded by the HTA programme as award number NIHR128996. The contractual start date was in February 2020. The draft manuscript began editorial review in January 2023 and was accepted for publication in August 2023. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' manuscript and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

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