


The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation

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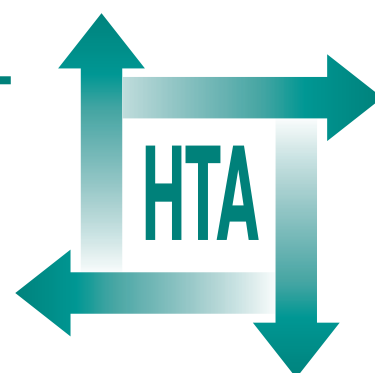
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Executive summary

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Executive summary

Background

Heart failure is an increasing health problem in England and Wales. Its incidence and prevalence are increasing, leading to frequent admissions to hospital and long-term drug costs. Concerns about the effects on the duration and quality of life of people and costs upon the NHS have resulted in several government policy initiatives. End-stage heart failure (ESHF) is associated with major disability and a poor prognosis. Heart transplantation has become the accepted form of treatment for people with ESHF, improving survival and patient quality of life. With continued decreases in organ donation in England and Wales, it is an option available to few. Mechanical circulatory support through left ventricular assist devices (LVADs) has attracted increased interest as an option for patients with ESHF whether as a bridge to heart transplantation (BTT), as a bridge to myocardial recovery (BTR) or as a long-term chronic support (LTCS). Continued developments of LVADs, declining costs and improvements in associated care have made their wider use a reality.

Objectives

The objectives of this study were to carry out a systematic review and an economic evaluation to examine the clinical and cost-effectiveness of LVADS as a BTT, BTR and LTCS for people with ESHF. The study focused on the effect of LVADs on the duration and quality of life of people with ESHF, the groups who may benefit from their use and assesses the implications for developing such a service within the NHS in England and Wales.

Methods

A systematic review of the evidence and an economic evaluation were undertaken using *a priori* methods.

Data sources

Eighteen electronic databases were searched from inception to October 2003. Bibliographies of related papers were assessed for relevant studies and experts and manufacturers were contacted to

identify additional published and unpublished references.

Study selection

Studies were included if they fulfilled the following criteria:

- **Interventions:** studies that evaluated currently available LVADs used as a BTT, BTR and LTCS for people with ESHF were considered for inclusion.
- **Participants:** people aged 16 years or older with ESHF and considered suitable for receipt of an LVAD as BTT, BTR or LTCS.
- **Outcomes:** survival, functional capacity [e.g. New York Heart Association (NYHA) functional classification, activities of daily living] and quality of life were the primary outcome measures considered within the systematic review.
- **Design:** systematic reviews, randomised controlled trials (RCTs), controlled clinical trials, cohort studies, case series, case studies, economic evaluations and cost studies were included.

Studies identified were assessed for inclusion through two stages with titles and abstracts and full papers of retrieved studies assessed by two reviewers, with differences in decisions resolved through discussion or through recourse to a third, independent reviewer.

Data extraction and quality assessment

Data were extracted by two reviewers using data extraction forms developed *a priori*, with any disagreements resolved through discussion or through recourse to independent assessment by a third reviewer. The methodological quality of the studies included in the systematic review of clinical and cost-effectiveness were assessed using recognised quality assessment tools using individual components of methodological quality rather than relying upon summary scores. The quality criteria used were applied by two reviewers, with any disagreements resolved through discussion or through recourse to a third, independent reviewer.

Data synthesis

Studies were synthesised using a narrative approach through subgroup analysis based on the indication for treatment, type of LVAD and quality of studies. ▶

Economic evaluation

The economic evaluation developed two models to evaluate the use of LVADs, first as a BTT and second as LTCS for patients suffering from ESHF. Insufficient data prevented the assessment of the use of LVADs as a BTR. The outcomes in the evaluation were assessed in terms of the benefits to patients (survival and quality of life) and costs incurred, with results presented in terms of a cost–utility analysis. Although medical therapy was the comparator treatment in the two models, the patients differed. Patients in the BTT model were those on the heart transplantation waiting list, whereas those in the LTCS model were excluded from the heart transplant waiting list owing to the severity of their condition. The models focused on those LVADs that were found in the systematic review to be clinically effective for the different indications and relevant to the UK setting.

Results

Clinical effectiveness of LVADs as a BTT for people with ESHF

Sixteen studies (one controlled clinical trial, five cohort studies with comparators, five cohort studies with no comparator, three case series and two case reports) assessed the clinical effectiveness of LVADs as a BTT, 11 studies of first-generation devices and five of second-generation devices. The methodological quality of the studies was generally weak, reflecting the quasi-experimental and observational study designs used and poor reporting of study characteristics. Despite the poor quality evidence, LVADs compared with other treatment options appeared to be beneficial for patients with ESHF when assessed using patient survival, functional status and quality of life. When compared with inotropic agents, LVADs appeared to provide a benefit in patient survival that increased with the length of support (difference in actuarial survival: 1 month 3%; 3 months 17%) and extended beyond heart transplantation (difference in actuarial survival: 1 year 24%; 4 years 30%). Comparisons of the use of LVADs with usual care were less certain, with outcomes varying from no difference in survival to, or after, heart transplantation, to improved survival for LVADs patients to heart transplantation (survival difference: range 14–59%) and post-transplantation (difference in actuarial survival: 1 and 2 years 100%). Studies of LVADs which did not include a comparator were often the only evidence available, particularly for the new devices. In these studies, implantation of an LVAD provided support for up to 390 days, with as many as 70% of patients

surviving to transplantation. Comparisons of different LVADs were limited. Only the HeartMate and Novacor LVADs were compared, with little difference in survival to transplantation. There was limited evidence assessing the effects of LVADs on the functional status and quality of life of patients with ESHF BTT. Patients supported by an LVAD appeared to have an improved functional status compared with those on usual care. Also, patients with an LVAD experienced an improvement in their quality of life from before implantation of the device to the period during support. The use of LVADs is associated with risks of adverse events, with patients suffering mechanical device failures, bleeding, thromboembolic events, infections, reoperations and psychiatric conditions. Adverse events rates varied between different LVADs and studies and some caution should be exercised in interpreting these results. With a scarcity of evidence directly comparing the different LVADs it is difficult, and perhaps inappropriate, to identify specific devices as the most clinically effective. However, the HeartMate LVAD is the only device that has evidence comparing it with several different alternatives, appearing to be more clinically effective than inotropic agents and usual care and as clinically effective as the Novacor device. Of the second-generation devices, the evidence suggests limited difference in the clinical effectiveness of the Jarvik 2000 and the MicroMed DeBakey LVADs. Although early in their development, these second-generation devices appear to show lower rates of adverse events, such as infection, bleeding and thromboembolism, which have affected the development and use of the first-generation devices. However, longer term outcomes are needed to ensure that these apparent benefits are maintained in practice and that the consequences associated with the non-pulsatile nature of the devices do not result in additional adverse events.

Clinical effectiveness of LVADs as a BTR for people with ESHF

Evidence of the clinical effectiveness of LVADs as a BTR for people with ESHF was limited to seven non-comparative observational studies (two case series and five case reports) of first-generation devices, which were judged to be of poor methodological quality. The seven identified studies appeared to show that the LVADs provided benefit in providing support for the patients until myocardial recovery. As there were no direct comparisons of different interventions, it is not possible to assess whether the LVADs are more effective than other alternatives or specific devices. No evidence was found to judge the

effects of the devices on the quality of life or functional status of patients. Limited information on adverse events was reported, although infections and bleeding were the main concerns.

Clinical effectiveness of LVADs as an LTCS for people with ESHF

Six studies (one RCT, one case series and four case reports) assessed the clinical effectiveness of LVADs as an LTCS for people with ESHF. Although the nature and methodological quality of the evidence varied between the different devices, it was evident that LVADs provided benefits for patients in terms of improved survival, functional status and quality of life. The REMATCH trial provided good-quality evidence that the HeartMate LVAD provided a statistically significant 48% reduction in the risk of death from any cause when compared with optimal medical management. Actuarial survival was significantly higher for patients with the HeartMate LVAD compared with optimal medical management at 1 year (52% versus 25%) and 2 years (23% versus 8%) follow-up. Importantly, improvements in 1-year survival were evident for patients aged under 60 years and those aged 60–69 years. Less rigorous evidence for the Novacor, Toyobo and Jarvik 2000 devices showed relatively high survival (90%), with patients supported for up to 4 years. Limited information on changes in patients' quality of life and functional status suggested that patients experienced improvements on specific scales following implantation of the HeartMate and Jarvik LVADs. Inevitably there are adverse events associated with the use of LVADs, with device malfunctions, infection and bleeding associated with their use. The HeartMate LVAD was associated with twice as many serious adverse events than optimal medical management, with significantly higher rates of non-neurological bleeding and neurological dysfunction. Other adverse events affected the different treatment options, whether devices or drug treatment. Despite these adverse events, the benefits of these LVADs appear to outweigh limitations. Evidence of the clinical effectiveness of the different devices indicates that the HeartMate LVAD appears to be effective when compared with optimal medical management. For the second-generation devices, the early evidence suggests that the Jarvik 2000 shows promise; however, further research is needed to assess whether these benefits are replicated in the longer term and whether there will be any long-term consequences associated with the change in the nature of the circulatory support.

Systematic review of the cost-effectiveness of LVADs for people with ESHF

Nineteen studies assessed the costs and cost-effectiveness of LVADs for people with ESHF, with the majority being simple costing studies and very few studies of the cost-effectiveness of LVADs. A number of the costing studies had serious methodological flaws. Even those judged of 'higher quality' had caveats limiting applicability and generalisability to a UK population. Significant limitations were the limited sample size and the lack of comparators against which to judge the significance of the reported costs. There was only one UK-based cost-utility analysis, which was populated with costs based on treatment protocols, data from individual NHS Trust finance departments and utilities derived from a US base study. The UK study reported cost per quality-adjusted life-year (QALY) values at the boundary of acceptability given recent decision-making. Based on total treatment costs of both LVAD BTT support and heart transplantation, the discounted cost per QALY was approximately £39,790 (range £28,510–74,000). Threshold analysis found that an LVAD device and procedure cost of £19,300 would equate to a cost per QALY of £20,000 or less.

Economic evaluation to assess the cost-effectiveness of LVADs for people with ESHF within the UK

The economic evaluation has shown that neither LVAD indication considered, that is, BTT and LTCS, is a cost-effective use. For the HeartMate LVAD used as a BTT the cost per QALY was £65,242. Stochastic simulation calculated the 95% confidence interval at £34,194 to £364,564. Only when the survival gain falls significantly does the cost-effectiveness rise to such upper bounds. A cost-effectiveness acceptability curve showed the likelihood of acceptability at current cost-effectiveness thresholds. The BTT indication approaches cost-effectiveness only when the one-off costs associated with an LVAD fall considerably. At a combined LVAD device and operation cost of £50,000 (compared with £87,877 in our model), the cost per QALY fell to approximately £40,000. Unfortunately, even assuming this eventuality, the BTT indication use parallels an ever-decreasing supply of donor hearts capping the ability of this innovative technology to yield widespread benefit. In the less restrictive indication, LTCS, where LVADs are not just given to patients awaiting transplantation, the analysis has shown that LTCS is not cost-effective. The baseline cost per QALY of the first-generation HeartMate LVAD was £170,616. One- and multi-way sensitivity analysis

had limited effect on the cost per QALY. A hypothetical scenario based on the cost of a second-generation MicroMed DeBakey device illustrated that a 60% improvement in survival over first-generation devices was necessary before the incremental cost-effectiveness approached £40,000 per QALY. Although the analyses recognise the benefits in terms of survival and quality of life, these are outweighed by associated increases in cost. Uncertainties remain, particularly with the lack of trial data on LTCS, research on second-generation devices and ongoing costs of medical management. The use of expert-based utilities in the LTCS data is also innovative but the sensitivity testing has shown this not to be an influential factor on cost-effectiveness at the margin.

Discussion and conclusions

Implications for practice

Although the systematic review of clinical effectiveness showed that LVADs are clinically effective as a BTT for people with ESHF, the economic evaluation indicated that they are not cost-effective. With the limited and declining availability of donor hearts for transplantation, it appears that the future of the technology is in its use as an LTCS. At present the evidence of clinical and cost-effectiveness of LVADs as an LTCS is less certain, particularly for the second-generation devices, and further study is needed. The limited research available showed some clinical benefit for patients receiving LVADs as an LTCS, but the economic evaluation suggested that they were not a cost-effective option. Limited numbers of patients with ESHF receive an LVAD within England and Wales and uncertainty remains about the potential need and demand that may exist. As a consequence, it is likely that there will be limited availability of clinical teams who can undertake these procedures and manage the patients subsequently and there would need to be a rapid increase in the training of staff and a step change

in the development of the necessary infrastructure. To provide the service to meet the needs of a conservative estimate of 3000 patients would result in a discounted cost to the NHS annually of £321 million. With less conservative estimates putting the potential need at between 7000 and 34,000 patients, the actual cost may be far higher.

Recommendations for future research

Although LVADs appear to be effective in improving the survival of patients with ESHF, whether as a BTT, BTR or LTCS, the methodological quality and strength of the evidence are poor. Further research is needed to examine the clinical effectiveness of LVADs for people with ESHF, assessing patient survival, functional ability, quality of life and adverse events. Although difficult to undertake with such fast-changing technologies, such evaluations should be RCTs and look at the head-to-head comparisons of different devices or usual medical care. Importantly, these studies should encompass the breadth of patient groups that may benefit from these devices. Evaluations of the clinical effectiveness of LVADs should include economic evaluations. It has become evident from this study that data for undertaking such studies are very limited. Data on quality of life, utilities, resources and costs are not readily available. Also, there is limited research on the epidemiology of ESHF and, as a consequence, it is difficult to establish the possible need and demand for the service. A systematic review of the epidemiology of ESHF should be undertaken to assess its potential impact.

Publication

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NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA Programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, service-users groups and professional bodies such as Royal Colleges and NHS Trusts. Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 01/12/02. The contractual start date was in June 2002. The draft report began editorial review in June 2004 and was accepted for publication in February 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. 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' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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