Clinical effectiveness and cost-effectiveness of second- and third-generation left ventricular assist devices as either bridge to transplant or alternative to transplant for adults eligible for heart transplantation: systematic review and cost-effectiveness model

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Scientific summary

Effectiveness of LVADs in adults eligible for heart transplantation
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Scientific summary

Background

Heart failure (HF) is a debilitating condition. Surgery and devices are costly. For the NHS to allocate and deliver its services, relative costs and benefits of various treatments need to be estimated. We aimed to investigate ventricular assist devices (VADs) used as a bridge to transplant (BTT) and as an alternative to transplant (ATT) for patients in the UK for patients with advanced HF who are eligible for heart transplant (HT). There are a number of newer devices and it is important to know the comparative cost-effectiveness of devices used in this way, relative to medical management (MM).

We know that historically HT has offered the best treatment option in terms of both length and quality of life (QoL) for these patients. However, HT is dependent on supply of donor hearts, whose availability appears to be diminishing while the design of VADs has been improving.

Research questions

In patients aged ≥ 16 years with advanced HF who are eligible for HT:

1. What is the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as a BTT compared with MM?
2. Where data permit, what is the clinical effectiveness and cost-effectiveness of second- and third-generation VADs used as an ATT in comparison with their use as a BTT therapy?

Objectives

1. To summarise previously published Health Technology Assessment (HTA) reports by Clegg *et al*. [Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*. The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation. *Health Technol Assess* 2005;**9**(45)] and Sharples *et al*. [Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*. *Evaluation of the ventricular assist device programme in the UK. Health Technol Assess* 2006;**10**(48)] on VADs.
2. To undertake a systematic review and evidence synthesis of the relevant clinical effectiveness and cost-effectiveness literature.
3. To further develop the cost-effectiveness and cost–utility models developed in the 2006 HTA: *Evaluation of the ventricular assist device programme in the UK* [Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*. *Evaluation of the ventricular assist device programme in the UK. Health Technol Assess* 2006;**10**(48)] and where possible to compare the use of VADs as a BTT first with MM and second as an ATT.
4. To investigate the factors that drive cost-effectiveness estimates.
5. To report on findings and make recommendations for future research.

Methods

Clinical effectiveness review methods

A systematic review of the evidence for each included VAD was undertaken following the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta Analyses statement.

The search strategy comprised the following main elements:

- searching of electronic bibliographic databases
- contact with experts in the field
- scrutiny of references of included studies
- screening of manufacturers' websites for relevant publications.

Databases included

Databases included MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Database of Systematic Reviews (CDSR); Database of Abstracts of Reviews of Effects (DARE); NHS Economic Evaluation Database (NHS EED); HTA databases [NHS Centre for Reviews and Dissemination (CRD)]; Science Citation Index and Conference Proceedings (Web of Science); UK Clinical Research Network Portfolio Database; Cumulative Index to Nursing and Allied Health Literature; PsycINFO; and the National Library of Medicine Gateway (US Meeting Abstracts and Health Services Research Projects in Progress). The following trial databases were also searched: Cochrane Central Register of Controlled Trials; Current Controlled Trials and ClinicalTrials.gov. In addition, the reference lists of relevant articles were checked, and the manufacturers' websites screened for relevant publications and other websites such as the Medicines and Healthcare products Regulatory Agency.

Inclusion criteria

Study design

- Studies with control groups [i.e. randomised controlled trials (RCTs), cohort studies, case–control studies], systematic reviews of studies with control groups.
- Case series were included if they included over 50 participants and were published in the last 5 years.

Population

- Participants (aged > 16 years) with advanced HF and considered suitable for receipt of a left ventricular assist device (LVAD), right ventricular assist device (RVAD) or biventricular assist device (BiVAD) as BTT or as potential long-term alternative to HT. Studies which reported BTT and destination therapy (DT) participants, but did not distinguish outcomes according to therapy, were included for purposes of completeness of information, but outcomes data were not included in the main text.

Intervention

- Second-generation axial continuous flow (CF) pumps.
- Third-generation bearingless CF pumps.
- LVAD, RVAD and BiVAD currently approved by the US Food and Drug Administration (FDA) and/or Conformité Européenne (CE) and in current clinical use in the UK as a BTT or as a potential long-term alternative to HT for participants with advanced HF.
- Studies with a mixture of different generation devices were considered if data for second- or third-generation devices could be identified separately from those for first-generation devices.

Comparators

- MM.
- Studies comparing HT with other interventions listed above.
- Studies comparing two different interventions listed above.
- Studies comparing first-generation devices with second- or third-generation devices were used to extract data on second- or third-generation devices only.

Outcomes

- Survival, functional capacity [e.g. change in New York Heart Association (NYHA) functional classification], QoL and adverse events.

Exclusion criteria

- Percutaneous ventricular assist device (PVAD) and total artificial heart (TAH).
- First-generation pulsatile volume displacement pumps.
- Devices yet to be FDA or CE approved.
- Devices for 'bridge to decision'.
- Studies not in English.
- Studies before the year 2003.

Searches were undertaken in March 2012.

Review methods

Quality criteria were applied independently by two reviewers using a recognised quality assessment checklist; disagreements were resolved by independent assessment by a third reviewer.

Methods of analysis/synthesis

Data were tabulated and discussed in a narrative review based on the type of VAD.

Cost-effectiveness review methods

A systematic review of cost-effectiveness publications of VADs was undertaken using the same search strategies and methods as the clinical effectiveness review but including relevant costs search terms. Data from the UK Blood and Transplant Database (BTDB) were obtained from the UK Transplant Registry maintained on behalf of the UK transplant community. The data set has been maintained as part of the National Specialist Commissioning Advisory Group (NSCAG) funded VAD programme and data are included from May 2002 to December 2011. The data are collected for patients from six UK centres (listed below) which are responsible for carrying out VAD implantation surgery:

- Royal Brompton & Harefield NHS Foundation Trust (RB)
- Papworth Hospital NHS Foundation Trust
- the Newcastle upon Tyne Hospital NHS Foundation Trust (NUT)
- the Glasgow Golden Jubilee National Hospital (GJNH)
- University Hospital of Birmingham NHS Foundation Trust (UNB)
- University Hospital of South Manchester NHS Foundation Trust (UHSM).

A semi-Markov multistate economic model was developed; the model was adapted from a previous HTA report and was updated with patient experience recorded in the UK BTDB during the period April 2005 to November 2011. The aim of the model was to estimate cost-effectiveness, first, of BTT relative to MM in patients with advanced HF and, secondly, of ATT relative to BTT in patients with advanced HF. The comparison of BTT with ATT represented a 'virtual' scenario to examine the impact of lack of availability of donor hearts. Model outputs are reported as incremental cost-effectiveness ratios (ICERs) as cost/

quality-adjusted life-year (QALY) gained and as cost/life-year gained (LYG). A discount rate of 3.5% was applied to both costs and benefits and time horizons of 3, 10 and 50 years (lifetime) were explored. The analyses were undertaken from the perspective of the NHS. A number of sensitivity analyses were undertaken varying survival in the MM control group (median survival ranged between 3.9 and 16.5 months) as well as other important input variables.

Results

Clinical effectiveness results

We identified 40 relevant publications. There were no randomised studies in our defined patient group (eligible for HT). The majority of included publications described single-arm prospective or retrospective case studies. No publication compared BTT outcomes with those for concurrent controls involving MM or best supportive care. Observations were often based on small numbers of patients from single centres who were participating in multicentre clinical studies. Overall, the study designs were not strong: studies were likely to be only moderately representative of underlying populations, there were no randomised trials and blinding of outcomes assessors was weak.

Analyses of included publications suggested the following estimates for baseline characteristics of participants in BTT studies: the majority were white (78–94%), male [84.2%, 95% confidence interval (CI) 79.4% to 88.0%] and middle aged [mean age was estimated at 50.8 years (95% CI 49.3 to 52.4 years)]. Mean body mass index (BMI) was estimated at 26.5 kg/m^2 (95% CI 25.7 to 27.3 kg/m^2); one-quarter of patients, 25.2% (95% CI 17.4% to 35.1%), were estimated to have diabetes mellitus; study participants had very severe HF with 83.5% (95% CI 78.0% to 87.9%) overall rated as NYHA class IV; most participants were supported with inotrope medication, 80.8% (95% CI 50.9% to 94.5%), and had low mean systolic blood pressure (BP), 97.3 mmHg (95% CI 92.8 to 101.7 mmHg).

By 12 months patients had suffered a variety of serious complications. Studies reported the following wide ranges for adverse events: 4–27% bleeding requiring transfusion; 1.5–40% stroke; 3.3–48% infection; 1–14% device failure; 3–30% HF; 11–32% reoperation; and 3–53% renal failure. Publications reported results from a variety of QoL and functional status measures. Statistically significant improvements in QoL and functional status were reported in studies of two devices [HeartMate II® (Thoratec Inc., CA, USA) and HeartWare® (HeartWare Inc., Framingham, MA, USA)]. There is still insufficient published evidence on second- and third-generation devices to draw robust conclusions about survival, adverse events and QoL for patients receiving these devices compared with MM without VAD.

UK Blood and Transplant Database individual patient data analysis

Using the UK BTDB, which has a large sample size reflecting UK practice, we identified 235 patients who had received a VAD. These patients were also mostly male, 80.4% (95% CI 74.77% to 84.99%), but were somewhat younger, mean age 44 years (95% CI 42.72 to 45.28 years), with a less severe NYHA class rating, class IV 58.1% (95% CI 39.07% to 75.45%), than in the published literature and were also more likely to be white, 89.7% (95% CI 81.80% to 90.86%), as compared with patients in published literature studies. Median survival with a VAD in this population was 32.1 months.

Just over three-quarters of these patients had been treated with inotropes prior to surgery, as compared with published BTT registry studies, which give slightly higher rates at 80%. In contrast, only just over 20% (307) of the 1496 UK BTDB MM patients were categorised as using inotrope treatment, supporting the use of the ‘inotrope’ subcategory of BTDB patients for the base-case (MM) comparator group in the economic model. Modelling of survival for these BTDB inotrope MM patients yielded a median survival of 9.1 months.

Cost-effectiveness results

- For research question 1, VADs used as BTT had higher mean costs in comparison with medically managed patients with higher survival and QoL benefits. This was the case for all the various scenarios examined for BTT patients and for all time horizons considered [3 years, 10 years and 50 years (lifetime)]. Probabilistic and deterministic results were confirmatory.
- In the base-case scenario for VAD patients compared with medically managed patients, the lifetime ICER was £55,173/QALY in the deterministic model. For a shorter time horizons of 3 years and 10 years the ICERs were £122,730/QALY and £68,088/QALY respectively. The base-case lifetime probabilistic ICER was £53,527/QALY.
- For research question 2, patient mean costs were lower for VADs used as ATT as compared with VADs used as BTT, but mean benefits were also reduced. Over the 3-year, 10-year and lifetime study horizons the ICERs (cost/QALY) were £353,467, £31,685 and £20,637 respectively (these ICERs are distributed in the 'south-west' quadrant of the cost-effectiveness plane); both costs and benefits for the VAD as ATT group were reduced relative to those for VAD as BTT. Probabilistic analysis confirmed these findings.

Conclusions and recommendations for future research

Our findings of a relative lack of cost-effectiveness for VADs as BTT relative to MM given standard levels of willingness to pay for a QALY in the NHS concur with those of other researchers. However, it is clear that devices are changing and improving and in the base-case analysis, cost-effectiveness over a lifetime horizon approaches that for interventions adopted by the NHS as end of life treatments. The cost of VADs would need to be reduced by 15% in order to bring the base-case lifetime time horizon ICER to £50,000 per QALY and by 76% to bring the ICER to £30,000 per QALY.

Future research

No RCT has been published allowing comparison of BTT with VADs versus MM. For ethical reasons a RCT offering equal probability of HT for each group would not be feasible. Therefore, attention should be directed towards:

1. How any future evaluations of second- or third-generation VADs might be conducted. Future studies should fully assess costs, long-term patient survival, QoL, functional ability and adverse events, so these may be incorporated into economic evaluation.
2. Agreement on outcome measures across future studies, in particular length of follow-up, time points for data collection, agreed QoL and functional ability measures.
3. Consideration of support for the UK BTBD so as to ensure that full and accurate records of all patients are kept, and that regular analyses and comparative assessments of performance with other international centres are undertaken.
4. Consideration of extending the UK BTDB data collection process so as to include QoL data [e.g. using the European quality of life-5 dimensions (EQ-5D)], and to include resource-use data in order to facilitate future cost-effectiveness evaluation.
5. Development of guidance in the use of VADs as technology and management continue to change. It will be important to monitor and update this assessment regularly.

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This report

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