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# A clinical and cost-effectiveness analysis of the HeartMate 3 left ventricular assist device for transplant-ineligible patients: A United Kingdom perspective

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**KEYWORDS:**
LVAD;
advanced heart failure;
HeartMate 3;
cost-effectiveness;
destination therapy

**BACKGROUND:** The clinical and cost-effectiveness of left ventricular assist device (LVAD) therapy for patients with advanced heart failure (HF) who are ineligible for heart transplantation is debated in the UK. This study develops an indirect comparison between the fully magnetically levitated HeartMate 3 (HM 3) LVAD and medical therapy (MT) to evaluate expected clinical and cost-effectiveness in the UK National Health Service (NHS) context.

**METHODS:** We performed an economic analysis comparing the HM3 pump against the HeartMate II LVAD (MOMENTUM 3), and then another analysis comparing MT with the first- and second-generation HeartMate XVE pump LVAD and HeartMate II LVAD for the same patient population (REMATCH and ROADMAP, respectively). By bridging those 2 analyses, an indirect comparison between HM3 and MT in the form of a network meta-analysis was developed. A literature search was performed to select the most appropriate pair of studies for this purpose. Outcomes were adjusted to produce Kaplan-Meier curves for the cost-effectiveness evaluation by using a decision-analytic model. Data were extrapolated linearly over a 5-year time horizon. Uncertainty and additional scenarios were addressed by one-way and probabilistic sensitivity analysis. Local costs and health utility were used from England, thereby representing the UK context.

**RESULTS:** The incremental cost-effectiveness ratio (ICER) for LVAD vs MT in transplant ineligible patients with advanced HF was estimated to be £47,361 per quality-adjusted life year gained, with a 97.1% probability of being cost-effective at £50,000. In a subgroup of patients who are inotropic therapy dependent (INTERMACS 1-3 severity profile), the ICER was £45,616, while for a population with less-ill ambulatory HF (INTERMACS profile 4-7) the ICER changed to £64,051.

*Abbreviations:* LVAD, Left Ventricular Assist Device; HF, Heart Failure; MT, Medical Therapy; HM3, HeartMate 3; NHS, National Health Service; ICER, Incremental Cost-Effectiveness Ratio; QALY, Quality-Adjusted Life Year; NICE, National Institute for Health and Care Excellence; HES, Hospital Episode Statistics; DT, Destination Therapy; BTT, Bridge to Transplant; CHEERS, Consolidated Health Economics Evaluation Reporting Standards; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MFF, Market Forces Factor; HRG, Healthcare Resource Group; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure; ROADMAP, Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients; MOMENTUM 3, Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3

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**CONCLUSIONS:** This study provides evidence that HM3 LVAD therapy in advanced HF patients ineligible for heart transplantation may be cost-effective compared to MT in the NHS UK-England context. The ICER is lowest for patients dependent on inotropic support, but exceeds the willingness to pay threshold of £50,000 in ambulatory noninotropic therapy dependent advanced HF patients.
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Heart failure (HF) is a major cause of hospitalizations in the UK.[1-4] According to the National Health Service (NHS) Hospital Admitted Care Activity, the number of emergency HF admissions increased from 81,000 in 2016/17 to 94,185 in 2019/20.[5,6] The estimated cost of HF hospital readmission ranges from £2,274 to £3,690 for an average length of stay of 6 to 9 days according to a National Institute of Health and Care Excellence (NICE) guidance and Hospital Episode Statistics (HES) database 2019/20.[7-9] As a result, the economic cost of HF is considerable, estimated at £2 billion in 2016. A 2021 report from the House of Commons shows that HF accounts for 2% of the total NHS budget, with 70% of these costs due to hospitalization.[4]

Advanced HF (AHF) describes a distinct group of patients with severe limiting symptoms and frequent HF hospitalizations associated with severe cardiac dysfunction despite conventional heart therapies and poor short-term prognosis.[10] Heart transplantation, limited by the scarcity of donors is an option for only a small subgroup of patients with AHF. Increasingly, LVAD has been used in transplant-ineligible patients with AHF for their remaining lifetime, referred to as destination therapy (DT).[11,12]

The clinical effectiveness and cost-effectiveness of LVAD therapy for AHF patients ineligible for heart transplantation is debated in the UK as well as worldwide. While Bridge-to-transplant (BTT) has been supported given the evidence available at the time of NHS England service specifications, DT has so far been explicitly excluded on the basis of lack of demonstration of cost-effectiveness[13] and absence of contemporary evidence around cost-effectiveness over Medical Therapy (MT) alone has not allowed for revision of the policy so far. First, direct comparison between LVAD and MT has only been studied with older generation LVADs, most that are no longer in clinical use.[14,15] Second, existing economic evaluations have shown poor cost-effectiveness owing to the suboptimal performance and decreased durability of the devices available at the time of such analyses,[16,17] and clinical and cost-effectiveness of LVAD has not been re-evaluated in light of the recent progress in LVAD therapy.[11] The latest advance in technology includes the HeartMate 3 (HM3) centrifugal-flow LVAD (Abbott, Chicago, USA), a fully magnetically levitated rotor pump with a superior clinical outcome compared to older generation devices. As evidence on its better performance and durability continues to grow, it is time to revisit the clinical and cost-effectiveness in the context of a more forgiving device that reduces the rates of hospitalizations and morbidity related to bleeding, stroke and need for surgical pump replacement.[18] This evaluation uses patient level evidence derived from robustly conducted clinical trials across various advanced heart failure populations to estimate the cost-effectiveness of LVADs compared to MT in patients with advanced HF, from an NHS UK-England perspective.

## Methods

### Model design

The economic analysis was performed by using a decision-analytic model to estimate clinical outcomes and costs among advanced HF patients receiving LVADs or MT (Figure 1), similar to previous studies.[17,19] A time horizon was 5 years post assessment for transplantation candidacy as this is the timescale used by NHS England Specialised Services and is plausible in terms of life expectancy as seen in outcomes from observational series of LVADs.[19,20] Costs and effects after year one were discounted at 3.5% per year, as recommended by NICE.[21] The model was constructed using Microsoft Excel. The economic evaluation was appraised using the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) checklist to ensure transparent reporting.[22]

### Data sources

We conducted a literature search using PubMed, which includes citations in MEDLINE, to search for articles about the cost-effectiveness of LVADs, excluding reviews, cost of illness studies and editorials. The search was limited to articles published in English-language journals from 2000 to 2020. Since the search did not yield a study on the HM3 LVAD specifically, we undertook an indirect comparison by utilizing the best available evidence to date for each arm. We first analyzed the HM3 pump against the HeartMate II LVAD (MOMENTUM 3 trial), and then another analysis comparing MT with either the HeartMate II LVAD for the same patient population (ROADMAP trial) or a first generation HeartMate XVE LVAD (REMATCH trial). By bridging those analyses, an indirect comparison is possible in the form of a network meta-analysis.[23] A schematic of the indirect comparison is depicted in Figure 1. The outcome values sourced through this step are used as input variables in the decision-analytics model to generate outcomes data for cost-effectiveness. A literature search was performed to select the most appropriate pairing of studies for this purpose.

HM3 LVAD was selected as the intended device comparator to MT since the overall survival and freedom from major adverse events are reported to be the greatest when compared with other devices in trial-level and real-world analyses.[24-26] The

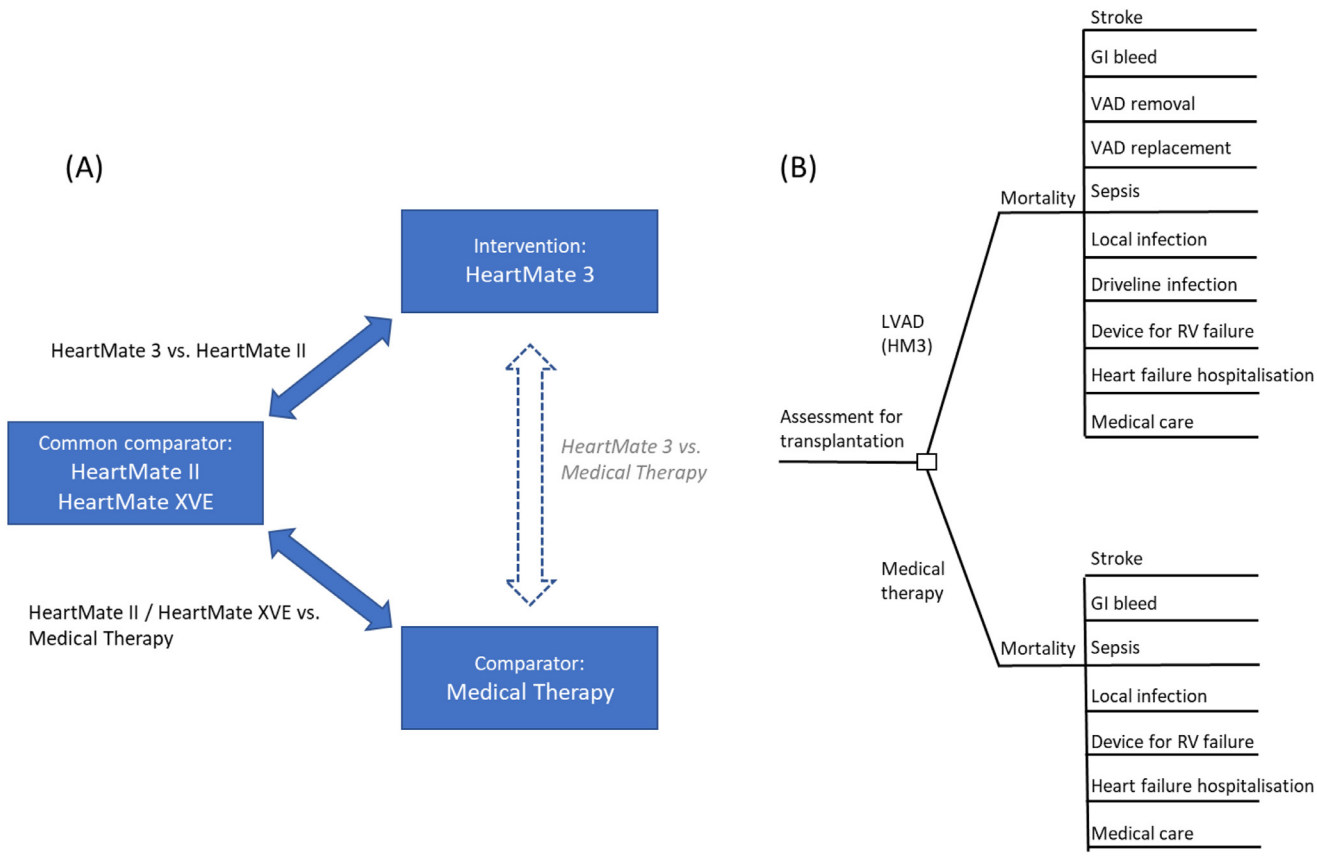


**Figure 1** Structure of the economic model. (A) The schematic of the network meta-analysis used to indirectly compare HeartMate 3 with Medical Therapy by mediating a common comparator (HeartMate II / HeartMate XVE). (B) The description of the decision-analytics model: the square represents a decision point and the model is run at a quarterly cycle over the time horizon of 5 years.

MOMENTUM-3 study was selected as the largest and most recent high-quality RCT to date for HM3, which explicitly pre-specified the examination of sub-group analyses in the DT-cohort compared with an older generation of the device.[26,27] Regarding the MT arm, the REMATCH trial or its sub-group analyses (in those restricted to inotropic therapy dependency) were chosen as were those in the ROADMAP trial because they used clinical endpoints comparable to MOMENTUM-3 and compared MT patients with a comparator, namely older generations of LVAD (HeartMate II in ROADMAP and HeartMate XVE in REMATCH), hence enabling an indirect comparison.[14,15] While clinical evidence, especially mortality, on the exact patient population was scarce, the validity of outcomes evaluated in the MT arm was verified in view of the current practice. A literature search confirmed that contemporary HF management with MT in the target population has not improved clinical outcomes appreciably and most gains in life expectancy with newer pharmacological therapy has been in those patients with chronic heart failure who maintain mild-moderate symptoms and have not transitioned to advanced stages.[28,29] For these reasons, recent cost-effectiveness analyses and reviews also used the REMATCH trial for developing the expected outcomes in the MT arm.[14,16,17] Given the evidence available, the outcomes of inotropic therapy bound patients have not improved since the time of REMATCH, and it can be considered as best available evidence for inotropic therapy bound patients (Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] 1-3 severity profile). The INTERMACS severity profile is a 7-stage classification developed in relation to population who can be considered for mechanical circulatory support, ranging from INTERMACS 1: critical cardiogenic shock, to INTERMACS 7: AHF with NYHA Class III symptoms.[29] The INTERMACS 1-3 patients are those dependent on inotropic therapy, while INTERMACS 4-7 are considered less ill and referred to as ambulatory AHF patients. For ambulatory non-inotropic bound patients, the best estimates for outcome are sequestered in ROADMAP and MedaMACS studies, and data reported in the ROADMAP trial were used for these stages of disease.[30-32] In order to account for the uncertainty and potential variability, sensitivity analyses were performed to allow for conservative estimates of benefit.

## Health outcomes

Patients receiving HM3 and MT were at risk for death, GI bleeding, stroke, infections (all infections, localized infections, driveline infections, and sepsis), and HF hospitalization. Age-specific mortality data were adjusted using English Life Tables to account for the proportion of people that would have been expected to die at a given age.[33]

Event rates and costs that populated the model were estimated for each quarter of a year, using 20 data points over the time horizon of 5 years each. Quarterly event probabilities for the HM3 group were estimated based on the Kaplan-Meier curves from the MOMENTUM-3 clinical trial data (Table 1).[27] We used the rate ratios from the REMATCH trial or the ROADMAP trial to estimate the corresponding event probabilities for the MT group (Table 1).[14] When explicit values were not available or reported, figures in the original manuscript were digitized for interpolation. Values beyond the 2-year follow-up period were linearly extrapolated using the last value (value at year 2) and by averaging the

**Table 1** Treatment Effect of Study Endpoints

| Year | Quarter | Adjusted survival[14,27] | | | | Freedom from stroke[14,27] | | Freedom from GI bleeding[14,27] | | Freedom from LVAD replacement or removal[26] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | LVAD (Taken from study) | LVAD (Age-adjusted) | MT (Taken from study) | MT (Age-adjusted) | LVAD | MT | LVAD | MT | LVAD | MT |
| 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | |
| 0.25 | 1 | 0.928 | 0.930 | 0.640 | 0.643 | 0.940 | 0.986 | 0.862 | 0.998 | 0.998 | |
| 0.5 | 2 | 0.888 | 0.892 | 0.455 | 0.462 | 0.932 | 0.984 | 0.821 | 0.998 | 0.988 | |
| 0.75 | 3 | 0.864 | 0.870 | 0.350 | 0.360 | 0.920 | 0.982 | 0.790 | 0.998 | 0.988 | |
| 1 | 4 | 0.837 | 0.850 | 0.246 | 0.260 | 0.906 | 0.978 | 0.765 | 0.997 | 0.988 | |
| 1.25 | 5 | 0.800 | 0.811 | 0.158 | 0.175 | 0.906 | 0.978 | 0.740 | 0.997 | 0.988 | |
| 1.5 | 6 | 0.783 | 0.796 | 0.110 | 0.131 | 0.890 | 0.975 | 0.720 | 0.997 | 0.988 | |
| 1.75 | 7 | 0.780 | 0.795 | 0.077 | 0.102 | 0.881 | 0.973 | 0.690 | 0.997 | 0.98 | |
| 2 | 8 | 0.767 | 0.785 | 0.073 | 0.102 | 0.881 | 0.973 | 0.668 | 0.996 | 0.972 | |
| 2.25 | 9 | | 0.779 | 0.000 | 0.033 | 0.877 | 0.972 | 0.635 | 0.996 | 0.964 | |
| 2.5 | 10 | | 0.771 | | 0.000 | 0.874 | 0.971 | 0.607 | 0.996 | 0.956 | |
| 2.75 | 11 | | 0.765 | | | 0.871 | | 0.579 | | 0.948 | |
| 3 | 12 | | 0.757 | | | 0.868 | | 0.551 | | 0.94 | |
| 3.25 | 13 | | 0.751 | | | 0.865 | | 0.523 | | 0.932 | |
| 3.5 | 14 | | 0.744 | | | 0.862 | | 0.495 | | 0.924 | |
| 3.75 | 15 | | 0.737 | | | 0.859 | | 0.467 | | 0.916 | |
| 4 | 16 | | 0.730 | | | 0.856 | | 0.439 | | 0.908 | |
| 4.25 | 17 | | 0.723 | | | 0.853 | | 0.411 | | 0.9 | |
| 4.5 | 18 | | 0.717 | | | 0.850 | | 0.617 | | 0.892 | |
| 4.75 | 19 | | 0.710 | | | 0.847 | | 0.645 | | 0.884 | |
| 5 | 20 | | 0.704 | | | 0.844 | | 0.673 | | 0.876 | |

| Year | Quarter | Freedom from Sepsis[14,26] | | Freedom from Localized Infection[14,26] | | Freedom from Driveline Infection[26] | | Freedom from Device for RV Failure[27,30] | | Freedom from Heart Failure Hospitalization[26,30] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | LVAD | MT | LVAD | MT | LVAD | MT | LVAD | MT | LVAD | MT |
| 0 | 0 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | | 1.000 | 1.000 | 1.000 | 1.000 |
| 0.25 | 1 | 0.893 | 0.947 | 0.799 | 0.877 | 0.977 | | 0.995 | 0.996 | 0.954 | 0.888 |
| 0.5 | 2 | 0.885 | 0.943 | 0.739 | 0.840 | 0.947 | | 0.990 | 0.993 | 0.927 | 0.775 |
| 0.75 | 3 | 0.878 | 0.940 | 0.708 | 0.821 | 0.916 | | 0.985 | 0.989 | 0.893 | 0.663 |
| 1 | 4 | 0.871 | 0.937 | 0.681 | 0.804 | 0.886 | | 0.980 | 0.986 | 0.884 | 0.550 |
| 1.25 | 5 | 0.865 | 0.934 | 0.649 | 0.785 | 0.855 | | 0.974 | 0.982 | 0.860 | 0.438 |
| 1.5 | 6 | 0.859 | 0.931 | 0.634 | 0.775 | 0.826 | | 0.969 | 0.978 | 0.851 | 0.325 |
| 1.75 | 7 | 0.854 | 0.928 | 0.612 | 0.762 | 0.796 | | 0.964 | 0.975 | 0.841 | 0.213 |
| 2 | 8 | 0.849 | 0.926 | 0.592 | 0.750 | 0.767 | | 0.959 | 0.971 | 0.841 | 0.100 |
| 2.25 | 9 | 0.844 | 0.923 | 0.571 | 0.737 | 0.738 | | 0.954 | 0.967 | 0.837 | 0.000 |

(*continued on next page*)

**Table 1** (*Continued*)

| Year | Quarter | Freedom from Sepsis [14,26] | | Freedom from Localized Infection [14,26] | | Freedom from Driveline Infection [26] | | Freedom from Device for RV Failure [27,30] | | Freedom from Heart Failure Hospitalization [26,30] | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | LVAD | MT | LVAD | MT | LVAD | MT | LVAD | MT | LVAD | MT |
| 2.5 | 10 | 0.839 | 0.921 | 0.551 | 0.724 | 0.708 | | 0.949 | 0.964 | 0.835 | |
| 2.75 | 11 | 0.834 | | 0.530 | | 0.679 | | 0.944 | | 0.831 | |
| 3 | 12 | 0.828 | | 0.509 | | 0.649 | | 0.939 | | 0.828 | |
| 3.25 | 13 | 0.823 | | 0.489 | | 0.620 | | 0.933 | | 0.825 | |
| 3.5 | 14 | 0.818 | | 0.468 | | 0.591 | | 0.928 | | 0.822 | |
| 3.75 | 15 | 0.813 | | 0.447 | | 0.561 | | 0.923 | | 0.819 | |
| 4 | 16 | 0.808 | | 0.427 | | 0.532 | | 0.918 | | 0.816 | |
| 4.25 | 17 | 0.803 | | 0.406 | | 0.503 | | 0.913 | | 0.813 | |
| 4.5 | 18 | 0.798 | | 0.386 | | 0.473 | | 0.908 | | 0.810 | |
| 4.75 | 19 | 0.793 | | 0.365 | | 0.444 | | 0.903 | | 0.807 | |
| 5 | 20 | 0.787 | | 0.344 | | 0.414 | | 0.898 | | 0.804 | |

change over the past 6 months (e.g., Q6 to Q7, and Q7 to Q8). Recent economic evaluations of LVAD extrapolated survival mostly in a linear fashion by assuming constant mortality rate in the several years after the last observation.[16,17,34] Data from earlier generations of LVADs have also shown a linear trend of survival between year 2 and 5 as analyzed in the INTERMACS database series of studies.[12] Reconstructed plots are shown in the Supplementary Materials.

There have been about 100 LVADs implanted per year in England in recent years. A recent report indicates 105 implants for 2018/19 and 84 implants in 2019/20.[34,35] With an assumption of 20% to 30% increased use attributable to the DT indication, expected annual costs for 20 to 30 patients were estimated, as this represents 4 to 6 patients per year per center in England.

## Utilities

Utilities are a quality-of-life measure that can be converted into quality-adjusted life years frequently used in economic analyses.[36] The utility values to describe patients with and without LVAD were taken from Sutcliffe et al,[37] who used a modelling of utilities for health states from patients in the Blood and Transplant Database, and are shown in Table 2. In the base case model, patients' pre-LVAD and receiving medical therapy were assigned a utility of 0.55. Patients' post-LVAD were assigned a utility of 0.74. A taper in quality of life was applied during the last 3 months of life from the 0.55 and 0.74 values above in the first month of the quarter, to 0.44 in the last month of the quarter. This was applied linearly, meaning that the second month values were 0.59 for LVAD and 0.50 for medical therapy. A taper value of 0.44 was chosen because this is the value reported for patients on medical therapy by Emin et al in a UK population.[38] A taper was applied because patients with heart failure are known to deteriorate over time.[39] The QALYs lost due to the taper in quality of life in the last 3 months of life were subsequently deducted from the total QALYs in the LVAD and MT groups.

## Costs

The costs associated with LVAD and MT are summarized in Table 2. Tariff values were used where possible because these reflect the costs borne by NHS England.[40] Critical care costs have been taken from the National Cost Collection for the NHS as an average for cardiac surgical adult patients at £1,800 per day.[41] A cost for assessment for transplantation candidacy was also included, which requires procedures such as cardiac catheterization, echocardiography, lung and kidney function tests, comprehensive blood tests, and outpatient follow-up visits so that the full costs of therapy options could be projected. The cost of mortality was based on the expected healthcare cost of heart failure patients in the last 3 months of life.[42] The estimate includes the cost of medications, primary and hospital healthcare costs.

Tariff values were multiplied by the Market Forces Factor (MFF) for each hospital trust in England that might undertake the procedure,[40] to provide an average cost. The hospital trusts were Newcastle upon Tyne Hospitals NHS Foundation Trust, University Hospitals Birmingham NHS Foundation Trust, Manchester University NHS Foundation Trust, Royal Papworth Hospital NHS Foundation Trust, and Royal Brompton & Harefield NHS Foundation Trust. The mean MFF was 1.1083. LVAD implantation was not described by tariff, but was costed as a complex, repair or replacement, of multiple heart valves, with complication and comorbidity (CC) Score 8+, elective value plus 5 days of critical

**Table 2** Costs and Utilities Used in the Economic Model

| Item | Mean value | Lower | Upper | Source |
|---|---|---|---|---|
| Assessment | £3,901 | £3,657 | £4,145 | 95% CI, Calculated from tariff values. |
| LVAD device | £80,000 | | | Market price estimate. Fixed cost. |
| LVAD implantation procedure | £28,223 | £26,460 | £29,985 | 95% CI, calculated from tariff values. |
| LVAD implantation follow-up | £917 | £859 | £974 | 95% CI, calculated from tariff values. |
| Mortality | £8,827 | £8,357 | £9,296 | Hollingworth et al [42]. 95% CI given. |
| Stroke year 1 | £13,452 | £9,416 | £17,488 | Xu et al [43]. Lower value = cost − (cost x 0.3). Upper value = cost + (cost x 0.3). |
| Stroke, each year, years 2-5 | £1,128 | £790 | £1,466 | Xu et al [43]. Lower value = cost − (cost x 0.3). Upper value = cost + (cost x 0.3). |
| GI bleeding | £2,239 | £2,099 | £2,379 | HRG FD03. Activity-weighted average. 95% CI, calculated from tariff values. |
| LVAD replacement or removal procedure | £29,682 | £27,829 | £31,536 | 95% CI, calculated from tariff values. |
| Sepsis | £8,260 | £7,744 | £8,776 | HRG WJ06. Activity-weighted average. 95% CI, calculated from tariff values. |
| Localized infection | £9.15 | £6.41 | £11.90 | NHS prescription cost [44] Lower value = cost − (cost x 0.3). Upper value = cost + (cost x 0.3). |
| Driveline infection | £9.15 | £6.41 | £11.90 | NHS prescription cost [44] Lower value = cost − (cost x 0.3). Upper value = cost + (cost x 0.3). |
| Device for right ventricular failure implantation (procedure and follow-up). | £58,700 | £55,034 | £62,366 | 95% CI, calculated from tariff values. |
| Device for right ventricular failure | £5,000 | | | Market price estimate. Fixed cost |
| Heart failure hospitalization | £10,108 | £9,477 | £10,740 | HRG EB03. Activity-weighted average. Plus 3 days of critical care. |
| Routine medical care per year | £864 | £605 | £1,123 | Griffiths et al [45]. Lower value = cost − (cost x 0.3). Upper value = cost + (cost x 0.3). |
| Medical therapy utility | 0.55 | 0.50 | 0.60 | Sutcliffe et al [37]. Linear taper for the last 3 months before death: fixed at 0.44. |
| Post-VAD utility | 0.74 | 0.59 | 0.89 | Sutcliffe et al [37]. Linear taper for the last 3 months before death: fixed at 0.44. |

care. The cost of death included inpatient and outpatient costs incurred from hospital episode statistics (HES) database, healthcare resource group (HRG), and national reference costs.[42] While this reflects some resource use cost in the last 3 months of life, it does describe healthcare costs associated with advanced heart failure mortality. The costs of stroke were taken from Xu et al[43] and were given for year 1 and subsequent years. An admission due to sepsis was costed as the activity-weighted tariff plus 2 critical care days. Driveline infections and localized infections were not described by tariff and were assumed to equal NHS prescription cost.[44] The cost of routine medical care was taken from Griffiths et al[45] and was assumed to be twice the cost listed in this publication to allow for end-stage heart failure to consume more resource.

## Sensitivity and uncertainty analyses

We conducted one-way deterministic sensitivity analyses to assess the relative impact of the event and cost parameters used in the model. Where upper and lower 95% confidence intervals were not given or not calculable, ± 0.30 of the base case was used to derive the upper and lower values.

As recommended by NICE guidance for England, a probabilistic sensitivity analysis was also undertaken,[21] using a gamma distribution to reflect uncertainties in costs and a normal distribution to reflect uncertainties in QALYs.[46] About 1,000 random draws were made from these distributions to estimate the proportion of ICERs that fell below a given willingness-to-pay threshold.[47]

## Results

The patient demographics of the studies used in this research are presented in Table 3. The outcome measures were mainly sourced from the DT cohort of MOMENTUM-3 study[27] and REMATCH trial,[14,15] and the ROADMAP trial[30] as appropriate respectively, for the LVAD arm and the MT arm. For those outcomes not available in the above studies, the next best options were used, namely the full cohort study of MOMENTUM-3 for LVAD replacement and infection. No interaction was observed between patient cohort groups of the MOMENTUM-3 trial regarding infection.[48] The ROADMAP study was used for device use in right ventricular (RV) failure and HF-related hospitalizations.[30,31]

**Table 3** Patient Demographics of Included Studies

| Demographic factors | MOM 3 (LVAD)[26] | MOM 3 - DT (LVAD)[27] | REMATCH (MT)[14] | ROADMAP (MT)[30] |
|---|---|---|---|---|
| Sample size (n) | 1,028 | 624 | 61 | 103 |
| Age (years) | 59 ± 12 | 63 ± 12 | 68 ± 8 | 66 |
| Male (%) | 80 | 82 | 82 | 71 |
| Ischemic cause of heart failure (%) | 42 | 47 | 69 | 50 |
| History of atrial fibrillation (%) | 42 | 47 | Not Stated | 35 |
| History of stroke (%) | 10 | Not Stated | Not Stated | Not Stated |
| Duration of HF > 1 yr (%) | Not Stated | Not Stated | Not Stated | 92 |
| Intravenous inotropes (%) | Not Stated | 86 | 72 | 0 |
| Previous cardiac surgical procedure (%) | | | Not Stated | Not Stated |
| Coronary-artery bypass | 20 | 26 | | |
| Valve replacement or repair | 7 | | | |
| LVEF (%) | 17 ± 5 | Not Stated | 17 ± 4.5 | Not Stated |
| Blood pressure (mm Hg) | | Not Stated | | Not Stated |
| Systolic | 109 ± 15 | | 103 ± 17 | |
| Diastolic | 67 ± 11 | | 62 ± 11 | |
| Mean arterial pressure (mm Hg) | 80 ± 10 | Not Stated | Not Stated | Not Stated |
| Heart rate (beats/min) | Not Stated | Not Stated | 84 ± 1.5 | Not Stated |
| Cardiac index (L/min/$m^2$) | 2.0 ± 0.5 | Not Stated | 2 ± 0.61 | 1.9 |
| Pulmonary-capillary wedge pressure (mm Hg) | 23.1 ± 9 | Not Stated | 25 ± 10 | 22 |
| Pulmonary vascular resistance (Wood units) | 3.1 ± 2 | Not Stated | 3.2 ± 1.8 | 3.3 |
| Right atrial pressure (mm Hg) | 11 ± 7 | Not Stated | Not Stated | |
| Aspartate aminotransferase (U/l) | Not Stated | Not Stated | Not Stated | 26 |
| Sodium (mmol/L) | 135 ± 4 | Not Stated | 135 ± 5.8 | |
| Creatinine (mg/dl) | 1.4 ± 0.4 | 1.4 ± 0.4 | 1.8 ± 0.7 | 1.3 |
| Albumin (g/dl) | Not Stated | 3.6 ± 0.5 | Not Stated | 4 |
| BUN (mg/dl) | Not Stated | 29.3 ± 13.6 | Not Stated | 28 |
| Estimated glomerular filtration rate (ml/min/1.73$m^2$) | 61 ± 24 | 57.6 ± 21.2 | Not Stated | 63 |
| Blood urea nitrogen (mg/dl) | Not Stated | 14 | Not Stated | Not Stated |
| 6 minute walk distance (m) | Not Stated | Not Stated | Not Stated | 219 |
| $VO_2$ max (ml/kg/min) | Not Stated | Not Stated | Not Stated | 9.7 |
| INTERMACS profile (%) | Not Stated | | Not Stated | |
| 1 | | 2 | | |
| 2 | | 30 | | |
| 3 | | 52 | | |
| 4 | | 14 | | 34 |
| 5-7 | | 1 | | 64 |
| Not provided | | 1 | | 2 |

The outcomes used in the analyses are shown in Table 1, showing the proportion of patients expected to incur each outcome at 5 years in the base case. Since the outcome values were reported at limited time points, the input values to the model were reconstructed using interpolation and extrapolation. For every outcome measure, the figures sourced directly from the evidence is shown, along with those "reconstructed." Those figures are blank, which are not relevant to the MT arm such as LVAD replacement, driveline infection, or survival after 2.5 years. None of the medical therapy patients are expected to survive to 5 years, as reported in REMATCH.[14,15] Table 4 shows the expected cost-effectiveness over 5 years. The incremental cost-effectiveness ratio (ICER) for LVAD vs medical therapy was estimated to be £47,361/QALY gained.

**Table 4** Cost-Effectiveness Results

| Treatment | Cost | QALYs |
|---|---|---|
| LVAD | £141,598 | 2.8307 |
| Medical therapy | £28,047 | 0.4331 |
| Incremental cost LVAD | £113,551 | |
| Incremental QALYs LVAD | 2.3976 | |
| ICER | £47,361 | |

## Sensitivity analyses

An additional scenario compared the HM 3 LVAD arm vs a subgroup of patients in MT arm, namely those patients who are dependent on inotropic therapy. Using the survival data from the REMATCH subpopulation, the ICER was £45,616/QALY gained. Similarly, the ICER using the survival data from the ROADMAP study, which included ambulatory noninotropic therapy advanced heart failure patients was £64,051/QALY gained. In the ROADMAP

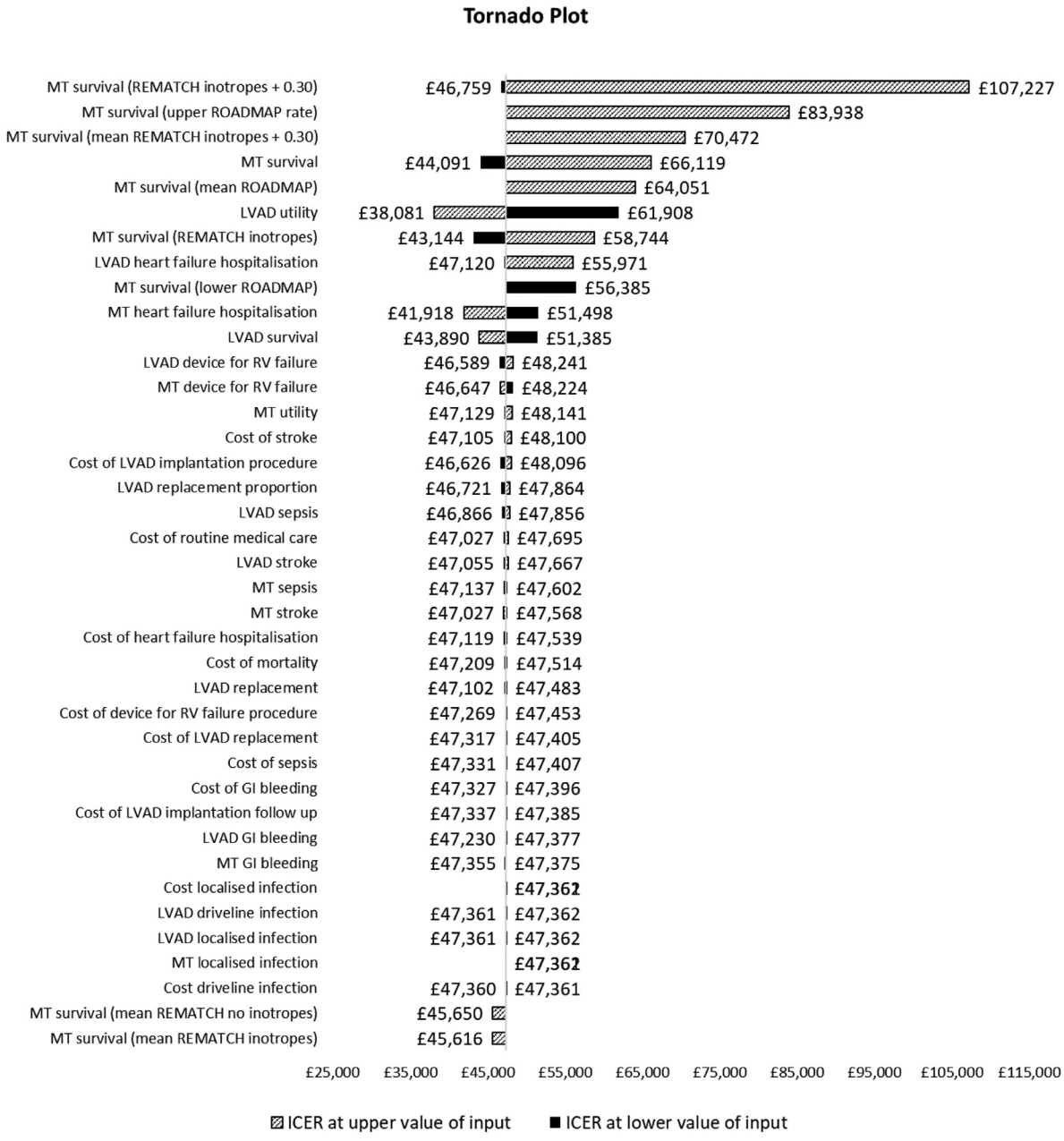


**Figure 2** Tornado plot showing expected ICERs at the lower and upper values of data inputs. ICER = incremental cost-effectiveness ratio; time horizon 5 years.

study, no patients were involved who were INTERMACS 1-3, and only included less ill ambulatory patients in INTERMACS 4-7,[30,31] hence simulating a patient profile with less advanced stage of HF. We also looked at varying the survival of the REMATCH inotrope-dependent population by 30% to account for the upper end of the 95% CI, which yielded an ICER of £70,472 (which denotes the upper boundary of the 95% CI estimate).

Figure 2 shows the Tornado plot that describes the results of one-way sensitivity analysis to account for uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. That is, the result of changing each of the base case values to their lower and upper values. Results were arranged such that higher ICERs were placed at the top of the plot. It can be seen that the economic model is most sensitive to survival and to the rate of HF hospitalization. The lower value of utility (a quality-of-life measure) of patients receiving LVAD therapy was the only other scenario in which the ICER was greater than £50,000/QALY gained.

Results of probabilistic sensitivity analysis are shown in Figures 3 and 4. Note that incremental cost is shown on the *x*-axis and incremental QALYs gained is shown on the *y*-axis. The mean probabilistic ICER was £41,514. The maximum incremental cost was £150,936 and the maximum incremental QALYs gained were 2.8688. The minimum ICER was £31,134 and the maximum ICER was £57,198. The probability of cost-effectiveness at £30,000/QALY

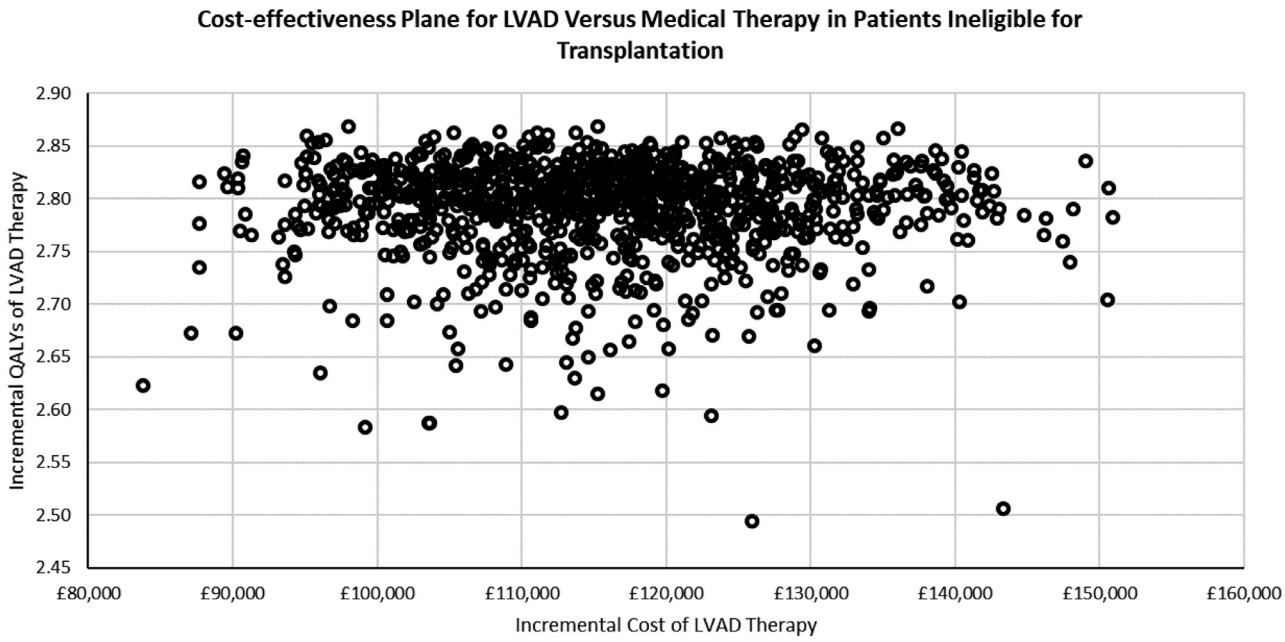


**Figure 3** Cost-effectiveness plane for LVAD vs medical therapy; time horizon 5 years.

gained (expressed as a percentage) was 0%, while the probabilities of cost-effectiveness at £40,000 and £50,000 were 36.3% and 97.1%, respectively.

If 20 to 30 heart transplant ineligible patients were treated with LVAD in England, the expected cost would be £2,831,960 to £4,247,940 over 5 years from the point of treatment, compared with an expected cost of £560,940 to £841,410 if the same patients were treated with medical therapy, respectively. This gives an expected incremental cost of £2,271,020 to £3,406,530 associated with the provision of LVAD therapy, with a total population QALY gain of 48.0 to 71.9 over 5 years.

## Discussion

This health economic analysis provides insight into the expected clinical effectiveness and cost-utility of LVAD therapy compared with medical therapy in patients with AHF who are ineligible for heart transplantation, cost-utility being assessed in the context of NHS England. The base-case scenario showed an ICER of £47,361/QALY gained for LVAD vs MT for patients who are ineligible for heart transplantation, which is below the end-of-life willingness-to-pay threshold of £50,000/QALY gained as generally accepted.[49,50] The high probability for cost-

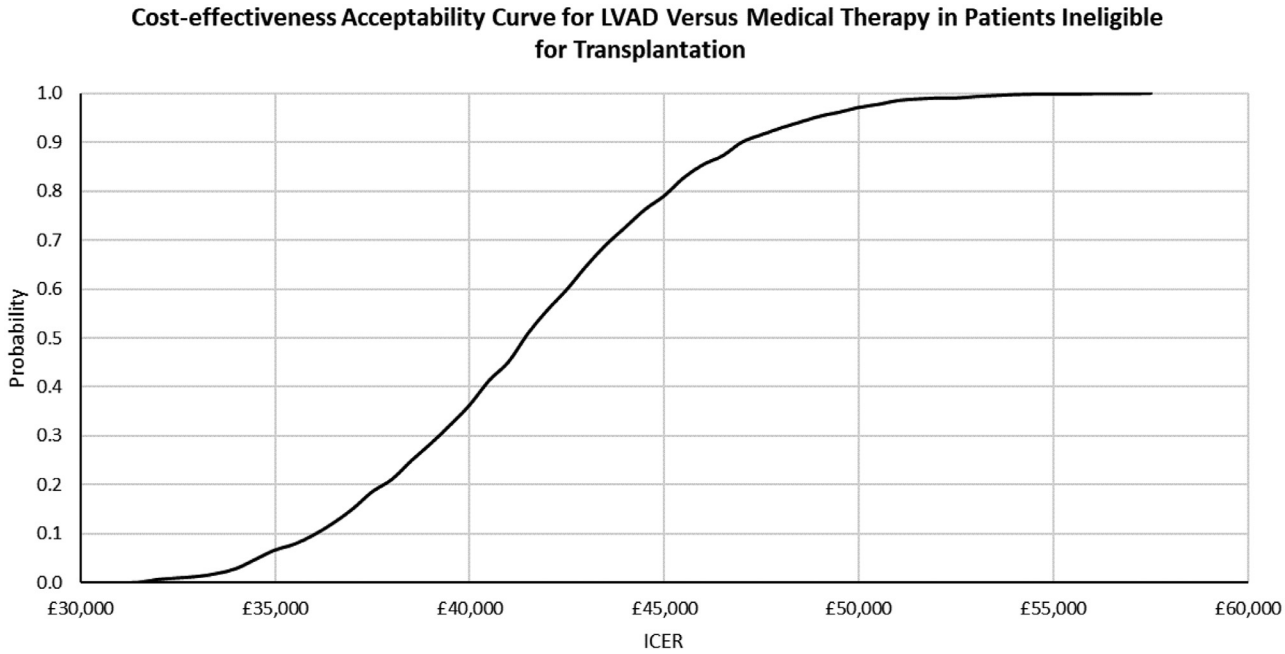


**Figure 4** Cost-effectiveness acceptability curve for LVAD vs medical therapy; time horizon 5 years.

effectiveness according to the probabilistic sensitivity analysis indicates that HM3 LVAD in DT use is a reasonable use of the NHS budget in those patients with AHF who do not have other viable alternatives.

In most European countries the intention of use (e.g., BTT or DT), and now even within the United States, is not a criterion for funding or reimbursement. In the United States, the Centers for Medicare and Medicaid Services (CMS) released the latest National Coverage Decisions in December 2020 that removed the therapeutic intent-to-treat criteria of BTT and DT on the basis of contemporary trials.[51] In contrast, the UK is one of the few regions where the payer continues to make clear distinction. The current NHS England service specifications only allow BTT, while DT is excluded.[52] Their policy proposition suggests that LVAD therapy should not be routinely commissioned because there is "not enough evidence of either clinical or cost-effectiveness to consider making this treatment available for a selected group of patients."[53] NHS England is currently looking into the cost-effectiveness of LVAD compared to medical therapy for DT in patients with AHF who are ineligible for transplantation.[54] Here, the payer's willingness-to-pay may be higher than the usually reported threshold of £20,000 to £30,000/QALY gain given the end-of-life nature of the therapy in the target population, and be set at £50,000.[49,50] This study has discussed the economic analysis on this unmet need and brought clarity with the best evidence available to date. Of note, while the ICER is over £30,000/QALY gained, end-of-life therapies may be recommended if they breach this value.[26,27] The incremental cost of LVAD therapy over medical therapy in 30 patients is expected to be £3,406,530, assuming this annual rate of use.

A number of economic evaluations have examined the cost-effectiveness of LVAD vs MT, and reported higher ICER at around US$ 200,000/QALY gained.[17,34,55] However, the current analysis differs from those previous studies, which were done in a non-NHS context (in USA or Canada), the evidence for the LVAD arm was not contemporary to the current situation of the therapy and time horizons differed. Recent real-world evidence showed that the HM3 LVAD improved survival and reduced adverse events, leading to concomitant reduction in costs by 17.4% to 26.1% compared to other LVADs in the US context, which demonstrates evidence of the progress of therapy toward cost-effectiveness in this field.[24] Another analysis for cost-effectiveness using a different centrifugal LVAD developed a Markov multiple-state economic model using NHS cost data. In this analysis, deterministic ICER was £46,207/QALY over a lifetime horizon.[56] Additionally, the CLEAR LVAD real-world analysis demonstrated that the outcomes and healthcare costs in the US context were lower for the HM 3 LVAD compared to the other centrifugal pump.[24] The present evaluation brings up-to-date information in the clinical and cost-effectiveness of LVAD for DT in patients not eligible for heart transplantation, particularly with reference to the HM3 LVAD.

This research had several limitations. First, the lack of direct comparison between LVAD for DT and MT in the context of recent clinical practice had to be addressed by developing an indirect comparison based on published literature pertaining to separate trials. Such indirect comparison of trials performed over 2 decades may be liable to biases that may not be accounted for however, for the specific population of patients who reach the point of inotropic therapy dependence; these estimates may still be relevant and accurate. Recent analyses have demonstrated the persistent dismal outcomes for patients, wherein it has been demonstrated that patients who preferred inotropic therapy over LVAD had median survival of 9.0 months and 2-year survival of only 38.4%.[28] It is possible that greater experience with LVAD therapy over time may contribute to better outcomes, which may result in a more favorable ICER. It is important to note that there is insufficient equipoise to replicate a direct comparison given the established survival benefit on LVAD therapy over medical therapy in AHF, even with less durable devices than the HM3 pump and especially in patients in INTERMACS 1-3 profile of severity (those requiring inotropic therapy). It should also be noted that despite advances in medical therapy, AHF by definition signifies a population that is poorly responsive to or deteriorating despite disease modifying pharmacological therapy. Most trials of pharmacological therapy therefore exclude these individuals. Hence there has not been a major improvement in survival simply by use of medical therapy in patients with advanced heart failure. The relevance of both arms was validated by choosing a common comparator (albeit LVADs of different generations) in between, and the relevance of the patient population as well as contemporality of the respective therapies were ensured by literature search and local practice. Second, the clinical outcomes were extrapolated beyond the time period originally reported in the literature. Linear extrapolation method was benchmarked with existing literature, and the outcome values using the quarter-year time steps were verified to match the survival data available from older generations of the LVAD therapy. This was reviewed from the INTERMACS analyses which looked at device related outcomes beyond 2 years and the linear slopes confirmed, although specific hazard ratios were not used due the analysis dominated by non-HM 3 LVADs.[12] Moreover, the comparability of patient groups across the studies used were not performed in a statistical manner since some demographic data were not reported. Third, the cost-effectiveness analysis considered freedom from the events in the decision-analytics model. However, the model provides a likelihood of an event happening (once or multiple times) to individuals at risk, based on rates in the population. The likelihood is zero if there is freedom from an event in the same population. Also, the bias would apply to both arms for the main events such as HFH, and its accelerated impact during the terminal phase of the patient has been accounted for by tapering health utilities as well as the cost of mortality so as to best represent the patient and outcomes trajectory within the given limitations of the model.

This analysis is based on costs under the single payer National Health System in the UK, and may not be directly translated into other healthcare systems. However, this analysis may be adapted for other healthcare systems using

the current health outcomes and utilities and the costs relevant to the healthcare system. Fourthly, other costs inherent to the delivery of LVAD therapy such as VAD coordinators, therapy services, additional Cardiologists and Surgeons have not been included. Similarly, the costs of supportive care in the medical therapy group such as social care support (carers, therapy services and specialist community and palliative care nurses) were not accounted for. Lastly, there is uncertainty around relevant cost items. For instance, Schueler et al used the cost of driveline infections and localized infections that were estimated higher than in our study, whereas this study included sepsis as a separate endpoint.[56] To account for uncertainty, sensitivity analyses were performed both one-way and probabilistically. Cost-effectiveness exceeds £50,000/QALY gained as patients become less sick, such as those in the ROADMAP trial and where survival in the medical therapy arm increases or survival in the LVAD arm decreases. This confirms the highest added value in those sickest group of patients (patients on inotropes) for whom heart transplantation is not an option, whereby the ICER showed stable cost-effectiveness in the NHS context.

In summary, we demonstrate that HM3 LVAD therapy in advanced HF patients ineligible for heart transplantation may be cost-effective compared to MT in the NHS UK-England context. The ICER is lowest for patients who are dependent on inotropic support; however, in ambulatory noninotropic therapy-dependent advanced HF patients, the ICER exceeds the willingness to pay threshold of £50,000, in the UK context.

## Disclosure statement

Hoong Sern Lim reports honoraria from Abbott and Abiomed. Steven Shaw reports honoraria from Abbott. Mandeep R. Mehra reports payments made to his institution from Abbott for consulting; Consultant fees from Medtronic, Janssen, Mesoblast, Portola, Bayer, Triple Gene, and Baim Institute for Clinical Research. Scientific Advisory Board Member for NuPulseCV, Leviticus and FineHeart.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2021.11.014.

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