Health Quality Ontario

Ontario Health Technology Assessment Series

Left Ventricular Assist Devices for Destination Therapy: A Health Technology Assessment

KEY MESSAGES

Left ventricular assist devices help keep blood flowing through the body by assisting a specific chamber in the hearts of patients with severe heart failure. A left ventricular assist device can be implanted as a last resort for patients with severe heart failure who cannot have heart transplantation; this is called destination (permanent) therapy.

Earlier devices used pulsing flow pumps to mimic the natural pulsing action of the heart. Later devices produced a continuous flow of blood into the arteries. Only a continuous-flow device is currently licensed by Health Canada for destination therapy. Pulsing flow pumps are no longer licensed by Health Canada for destination therapy.

We reviewed the medical and economic literature to find out whether continuous-flow left ventricular assist devices improve patient outcomes (for example, increase survival, improve quality of life, reduce adverse events) and offers value for money over optimal medical (drug) therapy.

One study compared pulsing flow pumps with drug therapy, and another study compared continuous-flow devices with pulsing flow pumps. We found no studies that compared continuous-flow devices with drug therapy; therefore we compared them indirectly.

Overall, for patients with end-stage heart failure who are ineligible for heart transplantation, the review found that permanent treatment with continuous-flow devices is effective at improving survival and quality of life compared with drug therapy. The review also found that permanent continuous-flow devices have higher adverse event rates than drug therapy. Although it improves survival and quality of life, the device itself and the surgery to implant it are very expensive.

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HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

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ABSTRACT

Background

Left ventricular assist devices (LVADs) provide circulatory support to assist the damaged left ventricle in patients with end-stage heart failure. Implantation of an LVAD is sometimes a last resort for patients with end stage heart failure who are ineligible for heart transplantation (destination therapy).

First-generation LVADs used pulsatile pumps to mimic the natural pulsing action of the heart. Implanted second-generation LVADs use a rapidly spinning rotor to produce a continuous flow of blood into the systemic arterial system.

Objectives

Our objectives were to:

- Determine the clinical effectiveness of LVADs for destination therapy for patients with end-stage heart failure who are ineligible for heart transplantation
- Estimate the cost-effectiveness of destination-therapy LVAD for patients with end-stage heart failure who are ineligible for heart transplantation and to estimate the potential budget impact for the Ontario Ministry of Health and Long-Term Care over the next 5 years

Methods

We performed a narrative review of the clinical and economic literature for effectiveness and cost-effectiveness and a budget impact analysis from the perspective of the Ministry of Health and Long-Term Care. We did not conduct a meta-analysis of the clinical evidence owing to differences in the type of LVADs included in the studies.

Results

Three systematic reviews and one observational study contributed to the clinical evidence. Three economic reviews contributed to the economic evidence. There is moderate quality evidence that treatment with continuous-flow LVADs improves survival but has higher adverse events rates compared with drug therapy. Low quality evidence suggests treatment with a continuous-flow LVADs improves quality of life. The incremental cost-effectiveness ratio associated with destination-therapy LVAD over optimal medical management is relatively high and exceeds the traditionally accepted thresholds ($50,000 to $100,000 per quality-adjusted life-year). The estimated net budget impact is $13.6 million in 2015, $20.7 million in 2016, $27.8 million in 2017, $35.8 million in 2018, and $45.0 million in 2019.

Conclusions

For patients with end-stage heart failure who are ineligible for heart transplantation, permanent treatment with continuous-flow LVADs is effective at improving survival and quality of life compared with drug therapy. However, permanent continuous-flow devices have higher adverse event rates than drug therapy. Although it improves survival and quality of life, the device itself and the surgery to implant it are very expensive.

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Objective of Analysis

This analysis aims to determine the clinical effectiveness of left ventricular assist devices (LVADs) for destination therapy for patients with end-stage heart failure who are ineligible for heart transplantation.

Clinical Need and Target Population

Description of Disease/Condition

Heart failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood. (1) The incidence of chronic heart failure is age dependent: from 20 per 1,000 persons 65 to 69 years of age to more than 80 per 1,000 persons 85 years of age or older. (1)

In Ontario, there were 419,551 incident cases of heart failure between 1997 and 2007, of which 216,190 patients required admission to hospital and 203,361 patients were treated as outpatients at the time of initial diagnosis. (2) Patients aged 65 years or older represented 80% of the overall cohort. (2)
Patients with chronic heart failure experience shortness of breath, a limited capacity for exercise, high rates of hospitalization and rehospitalization, and premature death. (3, 4) The New York Heart Association (NYHA) has provided a commonly used functional classification for the severity of heart failure (3, 5):

- Class I: No limitation of physical activity, no symptoms with ordinary exertion.
- Class II: Slight limitations of physical activity; ordinary activity causes symptoms.
- Class III: Marked limitation of physical activity; less than ordinary activity causes symptoms, asymptomatic at rest.
- Class IV: Inability to carry out any physical activity without discomfort, symptoms at rest.

Left ventricular assist devices can be used to provide circulatory support to assist the damaged left ventricle in patients with end-stage heart failure. Left ventricular assist devices can be used to provide temporary support while a patient waits for heart transplantation (bridge to transplantation). An LVAD can also be implanted as a last resort for patients with refractory heart failure who are ineligible for heart transplantation (destination therapy).

Table 1 outlines the intervention, comparator, population, and outcomes of interest for the economic analysis.

Table 1: Disease Interventions and Comparators Evaluated in the Economic Analysis

Intervention vs. Comparator	Patient Population	Outcomes of Interest
LVAD as DT vs. optimal medical management	Patients with end-stage heart failure, NYHA class IIIB/IV	Survival, functional status, quality of life, postoperative complications or device-related adverse events, cost-effectiveness, cost utility

Abbreviations: DT, destination therapy; LVAD, left ventricular assist device; NYHA, New York Heart Association.

Ontario Context

Left ventricular assist devices are funded by the Ministry of Health and Long-Term Care (MOHLTC). Table 2 shows the number of claims for "implantable ventricular assist device" (R704) over the last 5 years (Amy Martin, written communication, January 13, 2015). The schedule of benefit codes does not distinguish between LVADs and right ventricle assist devices; however, experts we consulted suggested that most R704 claims would be for LVADs.

Table 2: Number of Claims for "Implantable Ventricular Assist Device" (R704) in Ontario Over Last 5 Years

Fiscal Year	Paid Claims From Ministry	Diagnostic Codes*
2010	23	429, 428
2011	21	429, 428, 412, 746
2012	34	429, 428, 426, 746, 998
2013	22	429, 428, 426, 412, 746
2014	17	429, 746

Source: Amy Martin (written communication, January 13, 2015).

***Diagnostic Code Descriptions**

412	Old myocardial infarction, chronic coronary artery disease or arteriosclerotic heart disease, without symptoms
426	Heart blocks, other conduction disorders
428	Congestive heart failure
429	All other forms of heart disease
746	Other congenital anomalies of heart
998	Adverse Effects—of surgical and medical care

The diagnostic codes do not provide information regarding indications for LVAD implantation (i.e., bridge to transplant vs. destination therapy).

Currently, four hospitals provide LVADs as a bridge to transplant in Ontario (University Health Network, Ottawa Heart Institute, London Health Sciences Centre, and Hospital for Sick Children). (Trillium Gift of Life Network written communication, February 19, 2015).

Table 3 shows LVAD volumes for the last 4 fiscal years and projected volumes for the current fiscal year at each of the four Ontario hospitals.

Table 3: Volumes of Left Ventricular Assist Devices Implanted at Four Ontario Hospitals

Hospital	2012–2013 Funded Volume	2012–2013 Actual Volume	2013–2014 Funded Volume	2013–2014 Actual Volume	2014–2015 Funded Volume	2014–2015 Actual Volume
University Health Network	20	20	20	21	25	27
Ottawa Heart Institute	16	12	16	9	16	15
London Health Sciences Centre	6	3	6	3	6	5
Hospital for Sick Children	4	7	7	3	7	5

Source: Trillium Gift of Life Network (written communication, June 24, 2014).

Table 4 shows the patient status for the LVAD volumes reported to the Trillium Gift of Life Network in fiscal year 2013–2014. (Trillium Gift of Life Network written communication, February 19, 2015) For some patients, the potential for recovery or suitability for transplantation is uncertain. Bridge to candidacy refers to implantation of a device in order to clarify a patient's status and decide on a future strategy (device removal after recovery, cardiac transplantation, or destination therapy).

Table 4: Patient Status for LVAD Volumes Reported to the Trillium Gift of Life Network for Fiscal Year 2013–2014

Hospital	Total LVADs 2013–2014	Number of Patients Listed for Transplant	Number of Patients Not Listed for Transplant			
			Bridge to Candidacy	Bridge to Recovery	Died on Support	Unknown Reason
University Health Network	21	7	5	4	3	2
Ottawa Heart Institute	9	7	N/A	N/A	N/A	2
London Health Sciences Centre	3	3	N/A	N/A	N/A	N/A
Hospital for Sick Children	3	3	N/A	N/A	N/A	N/A

Abbreviations: LVAD, left ventricular assist device; N/A, not applicable.
Source: Trillium Gift of Life Network (written communication, February 19, 2014).

As of 2013, the Ministry of Health and Long-Term Care provides the following funding for each LVAD patient (Trillium Gift of Life Network written communication, February 19, 2015):

- adult $182,600
- child $223,400

Technology/Technique

The LVAD is implanted with the patient receiving general anesthetic and involves open-heart surgery. The pump component is placed in the pericardium. An inflow pipe is inserted into the left ventricle, and an outflow pipe is inserted into the systemic arterial system (usually the aorta). The power cable, which is attached to the pump, is brought through the abdominal wall to the outside of the body and attached to a control system and battery. The LVAD draws oxygenated blood from the left ventricle and pumps it into the systematic arterial system under pressure. (6)

First-generation LVADs used pulsatile pumps to mimic the natural pulsing action of the heart. Implanted second-generation LVADs use a rapidly spinning rotor to produce a continuous flow of blood into the systemic arterial system. (6)

This health technology assessment will examine the use of LVADs for destination therapy in patients who are ineligible for heart transplantation.

Regulatory Status

HeartMate II LVAS (Thoratec Corporation; Licence number 79765) is licensed by Health Canada as a Class IV device.

According to Health Canada, "the HeartMate II LVAS is intended for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure. The HeartMate II LVAS is also indicated for use in patients with NYHA Class IIIB or IV end-stage left ventricular failure who have received optimal medical therapy for at least 45 of the last 60 days, and who are not candidates for cardiac transplantation. The HeartMate II LVAS is intended for use both inside and outside the hospital, or for transportation of VAD patients via ground ambulance, fixed wing aircraft, or helicopter." (Health Canada written communication, December 16, 2014).

Research Questions

- What is the clinical effectiveness of left ventricular assist devices (LVADs) for destination therapy in patients with end-stage heart failure who are ineligible for heart transplantation?
    - mortality
    - adverse events
    - quality of life
- What is the economic impact of using LVADs for destination therapy in patients with end-stage heart failure who are ineligible for heart transplantation in Ontario?
- What are the cost utility and cost-effectiveness of left ventricular assist devices (LVADs) for destination therapy in end-stage heart failure patients who are ineligible for heart transplantation?
- What is the potential budget impact over the next 5 years for the Ontario Ministry of Health and Long-Term Care of LVADs for destination therapy in end-stage heart failure patients who are ineligible for heart transplantation?

CLINICAL EVIDENCE REVIEW

Objective

1. The objective of this study was to assess the effectiveness of left ventricular assist devices (LVADs) for destination therapy in patients with end-stage heart failure who are ineligible for heart transplantation?

    - mortality
    - adverse events
    - quality of life

2. What is the economic impact of using LVADs for destination therapy in patients with end-stage heart failure who are ineligible for heart transplantation in Ontario?

Methods

Literature Search Strategy

A literature search was performed on March 4, 2015, using Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database, for studies published from January 1, 2012, to March 5, 2015. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- published between January 1, 2012, and March 4, 2015
- observational studies, randomized controlled trials (RCTs), systematic reviews, and meta-analyses
- adult patients with end-stage heart failure who are ineligible for heart transplantation
- patients receiving an LVAD for destination therapy

Exclusion Criteria

- case reports, case series, letters to the editor
- patients who are eligible for heart transplantation
- patients with advanced heart failure receive an LVAD for purposes other than destination therapy

Outcomes of Interest

- mortality
- adverse events
- quality of life

Statistical Analysis

A meta-analysis was not performed because types of LVADs differed in various studies.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess the methodologic quality of systematic reviews. (7)

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (8) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that RCTs are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, three main factors that can raise the quality of evidence were considered: the large magnitude of effect, the dose-response gradient, and any residual confounding factors. (8) For more detailed information, please refer to the latest series of GRADE articles. (8)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect

Results of Clinical Evidence Review

The database search yielded 2,560 citations published between January 1, 2012, and March 4, 2015 (with duplicates removed). Articles were excluded on the basis of information in the title and abstract. Full texts of potentially relevant articles were obtained for further assessment. Figure 1 shows the breakdown of when and for what reason citations were excluded from the analysis.

Two studies (one systematic review (9) and one observational study (10)) met the inclusion criteria. The reference lists of the included studies and health technology assessment websites were hand-searched to identify other relevant studies, and two additional citations (two systematic reviews (6, 11)) were included, for a total of four studies.

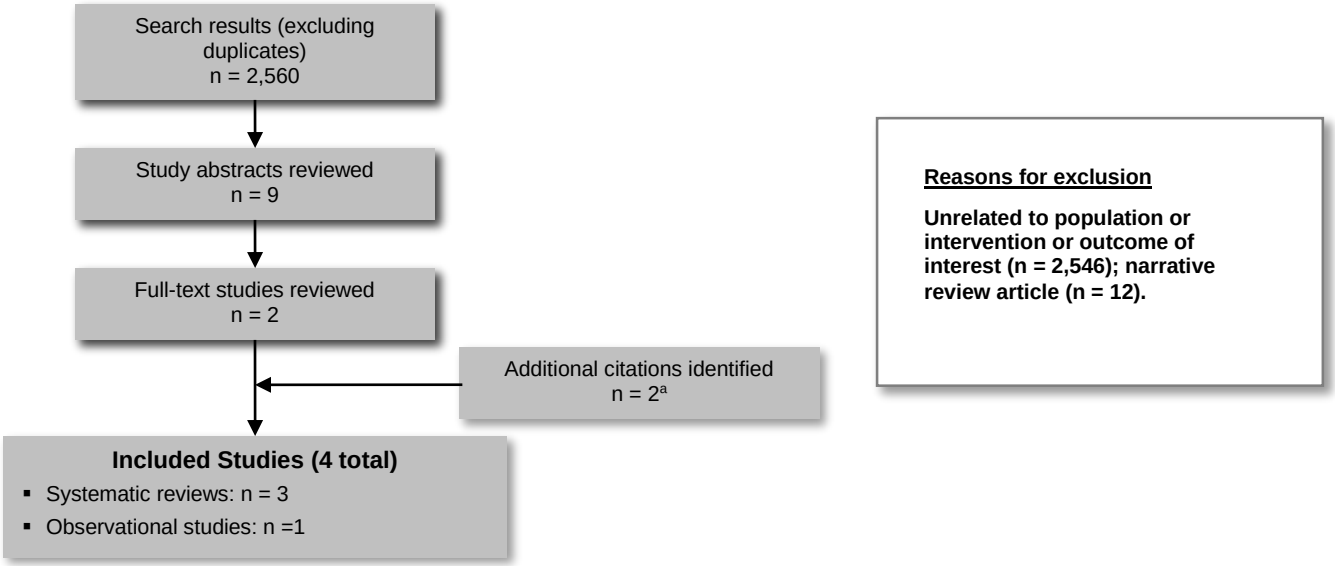

Figure 1: Citation Flow Chart for the Clinical Evidence Review

[a]Two systematic reviews.

Systematic Reviews

The AMSTAR scores for the systematic reviews are shown in Table A1.

Interventional Overview by National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (NICE) conducted a systematic review in 2015 to determine the effectiveness of LVADs for destination therapy among people ineligible for heart transplantation. (6) The literature search spanned to December 2014 and yielded one registry study, (12) 2 RCTs, (13, 14) two longer follow-up studies for each RCT, (15, 16) one nonrandomized comparative study, (17) and three case series (18-20) (N = 2,795 patients).

Included studies are summarized in Table A2. There are two main caveats regarding the literature:

- The studies included analyses of several types of LVADs (e.g., HeartMate II and HeartMate XVE). First-generation LVADs used pulsatile-flow pumps (e.g., HeartMate XVE). Second-generation LVADs (e.g., HeartMate II) produce a continuous flow of blood into the systemic arterial system.
- HeartMate II is currently the only LVAD licensed by Health Canada for destination therapy.

Heterogeneity and overlap of patients within the studies precluded a meta-analysis by NICE. Overall, NICE found the following. (6)

Efficacy

Survival

In an RCT (the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure [REMATCH] trial) of 129 patients treated by pulsatile-flow LVAD (n = 68) or optimal medical management (n = 61), survival rates were 23% and 8% respectively, at 2-year follow-up (*P* = .09). (17) In a longer follow-up of the same study, survival rates were 16% in patients receiving pulsatile-flow LVADs and 8% in patients receiving optimal medical management at 4-year follow-up (no *P* value reported). (16)

In a registry of 1,287 patients treated by continuous-flow (n = 1,160) or pulsatile-flow (n = 127) LVADs, survival rates were 76% and 68%, respectively, at 1-year follow-up (*P* < .0001). At 2-year follow-up, survival rates were 67% in continuous-flow patients and 45% in pulsatile-flow patients (*P* < .0001). In the same study, survival to device exchange or death secondary to device malfunction was 96% in continuous-flow patients and 83% in pulsatile-flow patients at 1-year follow-up (no *P* value reported). (12)

Recovery

In the registry of 1,287 patients treated by continuous-flow LVADs or pulsatile-flow LVADs, recovery from heart failure allowing for device removal was reported in 0.2% (3/1,287) of all patients. (12)

Six-Minute Walking Test

In an RCT of 200 patients treated by continuous-flow (n = 134) or pulsatile-flow (n = 66) LVADs, 6-minute walking test distances improved from 182 to 318 m (*P* < .001) and 172 to 306 m (*P* < .001), respectively, at 1-year follow-up (*P* value between groups = .22). (13)

Quality of Life

In the RCT of 200 patients treated by continuous-flow or pulsatile-flow LVADs, mean scores from the Minnesota Living With Heart Failure Questionnaire (MLHFQ) (which range from 0 to 105; lower scores indicate better quality of life), improved from 75.4 to 34.1 ($P < .001$) and 76.1 to 44.4 ($P < .001$), respectively, at 1-year follow-up (P value between groups = .03). In addition, mean overall scores from the Kansas City Cardiomyopathy Questionnaire (which range from 0 to 100; higher scores indicate better quality of life) improved from 27.4 to 65.9 ($P < .001$) in continuous-flow patients and from 46.5 to 59.1 ($P < .001$) in pulsatile-flow patients at 1-year follow-up (P value between groups = .06). (13)

In the RCT of 129 patients treated by pulsatile-flow LVADs or optimal medical management, mean scores from the MLHFQ improved from 75 to 41 and 75 to 58, respectively, at 1-year follow-up (P value between groups = .11). (14)

Emotional Impact

In the RCT of 129 patients treated by pulsatile-flow LVAD or optimal medical management, mean emotional domain scores (which range from 0 to 100; higher scores indicate better emotional outcomes) on the 36-item Short Form Health Survey (SF-36) changed from 33 to 64 and from 25 to 17, respectively, at 1-year follow-up (P value between groups < .05). In addition, mean Beck Depression Inventory scores (which range from 0 to 64; lower scores indicate less depression) improved from 19 to 8 in pulsatile-flow patients and from 16 to 13 in patients receiving drugs at 1-year follow-up (P value between groups < .05). (14)

Safety

Death Related to Device Failure or Malfunction

Death caused by device failure was reported in less than 1% (6/1,160) of patients treated by continuous-flow LVADs and 2% (3/127) of patients treated by pulsatile-flow LVADs, at 2-year follow-up, in a registry of 1,287 patients. (12)

Death from loss of power to external components of LVADs was reported in 2% (9/414) of patients at a minimum follow-up of 2 years in a case series of 414 patients treated by continuous-flow LVADs. (15)

Neurologic Events

Ischemic stroke was reported in 8% (11/133) of patients treated by continuous-flow LVADs and 7% (4/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in an RCT of 200 patients ($P = .38$). Hemorrhagic stroke was reported in 11% (15/133) of patients treated by continuous-flow LVADs and 8% (5/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up ($P = .33$). (13)

Neurologic events, such as transient ischemic attacks, seizures, and confusion, were reported in 12% (48/414) of patients at a minimum follow-up of 2 years in the case series of patients treated by continuous-flow LVADs. (15)

Right-Sided Heart Failure

Right-sided heart failure, managed by extended inotrope therapy, was reported in 20% (27/133) of patients treated by continuous-flow LVADs and 27% (16/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in an RCT of 200 patients ($P < .001$). Right-sided heart failure, treated by right ventricular assist devices, was reported in 4% (5/133) of

patients treated by continuous-flow LVADs and 5% (3/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up (*P* = .12). (13)

Failure

Respiratory failure was reported in 38% (50/133) of patients treated by continuous-flow LVADs and 41% (24/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in an RCT of 200 patients (*P* < .001). (13)

Device-Related Infection

Left ventricular assist device–related infection was reported in 35% (47/133) of patients treated by continuous-flow LVADs and 36% (21/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in an RCT of 200 patients (*P* = .01). (13)

Driveline infection was reported in 28% (117/414) of patients at a minimum follow-up of 2 years in the case series of 414 patients treated by continuous-flow LVADs. (13)

Non–Device-Related Infection

Local infection was reported in 49% (65/133) of patients treated by continuous-flow LVADs and 46% (27/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in an RCT of 200 patients (*P* = .02). No additional details were provided. (13)

Sepsis

Sepsis (no further details provided) was reported in 36% (48/133) of patients treated by continuous-flow LVADs and 44% (26/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in an RCT of 200 patients (*P* < .001). (13)

Pump Replacement

Pump replacement was needed for 9% (12/133) of patients treated by continuous-flow LVADs and 34% (20/59) of patients treated by pulsatile-flow LVADs at 2-year follow-up in an RCT of 200 patients (*P* < .001). (13)

Pump Thrombosis

Pump thrombosis was reported in 4% (5/133) of patients treated by continuous-flow LVADs and no patients treated by pulsatile-flow LVADs at 2-year follow-up in an RCT of 200 patients (no *P* value reported). (13)

Pump thrombosis was reported in 5% (21/414) of patients at a minimum follow-up of 2 years in the case series of 414 patients treated by continuous-flow LVADs. (13)

Bleeding

Bleeding that needed blood transfusion was reported in 76% (315/414) of patients at a minimum follow-up of 2 years in the case series of 414 patients treated by continuous-flow LVADs. Bleeding that needed surgical re-exploration was reported in 23% (95/414) of patients (no further details were provided). (15)

Validity and Generalizability of Studies Included in Systematic Review

- Some studies were follow-up studies (15, 16) of RCTs, (13, 14) and other studies employed secondary data analysis. (17)

- Cardiac-related adverse events and causes of death were tabulated as categorized by the authors. It could be argued that these should be reported as efficacy outcomes; however, authors presented Kaplan-Meier estimates as key efficacy outcomes. Cardiac-related death rates could not be easily compared with Kaplan-Meier estimates, so the NICE team adopted the authors' approach to avoid confusion.
- Results could be prone to bias because they were obtained from several cardiac centres where different clinicians were reporting outcomes. There may have been differences in the way data on outcomes were obtained from the various study groups. (12-18)
- The longest follow-up period reported was 4 years. (15)
- The largest available study included a small proportion of patients (2.4% [31/1,287]) treated by destination therapy using bi-ventricular assist devices in the analyses. (12) However, NICE considered it unlikely that inclusion of these patients would have resulted in overestimations or underestimations of the treatment effect.
- Several studies reported the occurrence of adverse events as incidence rates (rate per patient time) rather than as cumulative incidences. (12, 14, 20)
- All included studies used Kaplan-Meier survival curves to evaluate survival.
- More recent studies predominantly focused on evaluating the safety and efficacy of continuous-flow LVADs. (12, 13, 15, 17)
- One study did not stratify results according to device type8. (19)
- Authors have suggested that, in light of recent developments, LVAD destination therapy could be suitable for some patients who are also eligible for transplantation.

Systematic Review by Boothroyd et al

In Canada, Boothroyd et al (9) systematically reviewed the evidence on the clinical effectiveness of two types of continuous-flow LVADS (HeartMate II and HeartWare) for bridge-to-transplant and destination-therapy patients. However, only HeartMate II is currently licensed for destination therapy by Health Canada.

The literature search spanned January 1, 2008, to June 15, 2012. The systematic review was categorized according to transplantation eligibility and device. For patients ineligible for heart transplantation who received the HeartMate II LVAD, three studies were identified. (13, 15, 21) Two of these studies were included in the systematic review by NICE. (13, 15)

The study by Petrucci et al. (21) was a substudy of the trial by Slaughter et al, (13) and the objective was to examine neurocognitive function in destination-therapy patients receiving continuous-flow versus pulsatile-flow LVADs. Twelve of the 35 trial sites were selected to perform neurocognitive assessments in their patients. The 12 sites were selected to represent a range of volume experience in implanting and managing LVAD patients. Neurocognitive assessments were performed at 1, 3, 6, 12, and 24 months after LVAD implantation in a total of 126 patients of the 850 enrolled in the original trial. (13) Overall, Boothroyd et al stated that neurocognition was stable or improved at 6 months and 2 years for the subgroup of patients who received continuous-flow LVADs.

Limitations to the study by Petrucci et al (21) included:

- substudy of the investigation by Slaughter et al (13)
- because neuropsychologists were available at only three of the sites for the neurocognitive examinations, LVAD nurse coordinators and research coordinators were designated as examiners after training and "demonstrated reliability." Examiner bias could have been

introduced with the different testers at different sites. Petrucci et al stated, “However, there were too few patients to conduct a meaningful analysis to determine possible effects” (21)
- lack of a control group or baseline neurocognitive measurements
- lack of information regarding other factors that affect neurocognitive function in LVAD patients (e.g., patient hemodynamics, medications, metabolic values, central nervous system depressants, psychotropic drugs, or emotional state) (21)
- dropouts or missing data: At 1 month, 84 to 94 HeartMate II patients were assessed for various neurocognitive domains. At 24 months, HeartMate II patients assessed for neurocognitive domains ranged from 33 to 36 (21)
- manufacturer provided study data and statistical analysis (21)

Overall, Boothroyd et al (9) concluded:

- “Evidence is sufficient to support LVAD use (1-year survival reaching 78% for destination therapy compared with 25% for medical therapy), regardless of transplantation eligibility status as long as patients are carefully selected and program infrastructure and budget are adequate. However, evidence gaps, limitations in economic models and the lack of Canadian data point to the importance of mandatory, systematic monitoring of LVAD use and outcomes.”
- Bridge-to-transplant and destination therapy as implantation strategies are no longer mutually exclusive and can be difficult to assign.
    - The most recent Interagency Registry for Mechanically-Assisted Circulatory Support (INTERMACS) annual paper (22) reported that mechanical circulatory support (which includes LVADs, right ventricular assist devices, biventricular assist devices, and total artificial hearts) as destination therapy represents a large proportion of overall implants. In the United States, the proportion of patients receiving a mechanical circulatory support device as destination therapy increased from 14.7% in 2006–2007 to 41.6% in 2011–2013. (22) The proportion of patients listed for cardiac transplant at the time of implant decreased from 42.4% (2006–2007) to 21.7% (2011–2013). (22) When continuous-flow devices were examined in isolation, the same trends persisted for patients listed for transplant at implant and those receiving devices for destination therapy (Table 5). (22)

Table 5: INTERMACS Registry of Continuous-Flow Left Ventricular Assist Devices and Biventricular Assist Devices Implanted From 2008 to 2013 (N = 9,371)

Device Strategy at Time of Implant	**2008–2010** N (%)	**2011–2013** N (%)	**Total** N (%)
BTT	1,133 (39.0)	1,342 (26.4)	2,475 (26.4)
BTC			
BTT likely	765 (26.3)	1,387 (21.5)	2,152 (23.0)
BTT moderate	296 (10.2)	663 (10.3)	959 (10.2)
BTT unlikely	82 (2.8)	218 (0.75)	300 (3.2)
DT	591 (20.3)	2,781 (43.0)	3,373 (36.0)
BTR	15 (1.0)	31 (1.0)	46 (1.0)
Rescue therapy	10 (0.3)	17 (0.3)	27 (0.3)
Other	14 (0.5)	26 (0.4)	40 (0.4)
Total	2,906 (100.0)	6,465 (100.0)	9,371 (100.0)

Abbreviations: BTC, bridge to candidacy; BTR, bridge to recovery; BTT, bridge to transplant; DT, destination therapy; INTERMACS, Interagency Registry for Mechanically-Assisted Circulatory Support.

Systematic Review by US Department of Veterans Affairs

In 2012, the US Department of Veteran's Affairs systematically reviewed the use of current-generation LVADs as destination therapy. (11) The literature search spanned 1995 to October 2011. Overall, four studies were identified; the RCT by Slaughter et al, (13) an update of the INTERMACS registry study by Kirklin et al, (23) a longer follow-up of the RCT by Park et al, (15) and a retrospective case series by Struber et al (24) examining the outcomes of the first 101 destination and bridge-to-transplant therapy patients in Europe.

The case series by Struber et al (24) contained 31 patients who received destination therapy using a continuous-flow LVAD. Limitations to the study included:

- small retrospective unblinded case series
- no control group
- no description of baseline characteristics
- no description of the follow-up
- selection of patients for destination therapy was not described

Overall, the Veterans Affairs systematic review found the following (11):

- Only one good-quality RCT of a newer-generation continuous-flow LVAD as destination therapy has been reported to date. This study found that patients who received the HeartMate II had better survival, developed fewer major complications, spent less time in the hospital, and had substantially less adverse effect from heart failure on their quality of life than those who received the older-generation pulsatile-flow HeartMate XVE device.
- Currently, selection of patients for destination therapy is based on the Food and Drug Administration (FDA)–approved indication and Centers for Medicare and Medicaid Services (CMS) criteria for coverage of Medicare beneficiaries that are based on enrollment criteria used by pivotal RCTs. Studies have not validated use of other preoperative variables to further refine patient selection and thereby improve patient outcomes.

Veterans Affairs made the following conclusions (11) and graded them using the method by Owens et al. (25)

- Use of the FDA-approved HeartMate II rather than the HeartMate XVE LVAD results in superior patient outcomes (better survival and daily existence, fewer harmful complications) (moderate-strength evidence).
- Preoperative correlates of patient outcomes have not been established as patient selection criteria that can lead to better patient outcomes (insufficient evidence).

One recent observational study was identified in the literature search. (10) Jorde et al (10) conducted an FDA postapproval study to determine whether results with the HeartMate II continuous-flow LVAD in a commercial setting were comparable to results during the destination therapy multicentre clinical trial by Slaughter et al (historical control group). (13)

For the historical control group, data were retrieved from the original clinical trial database (same population as Slaughter et al). (13) For the postapproval group, data were obtained from the INTERMACS registry during the time frame of 2005 to 2007 (same population as Kirklin et al). (12)

Patients receiving mechanical circulatory devices in the United States who are entered into INTERMACS must fulfill two criteria: (a) device must be FDA approved; and (b) patient must provide informed consent for entry of data into INTERMACS. (12) For FDA-approved devices, INTERMACS receives data on device implant and survival/mortality at 48 hours for all patients, even if consent is not obtained. (12) Further follow-up is available only if patient consent is obtained. Approximately 10% of patients suitable for INTERMACS were not entered with full data collection because of failure to obtain informed consent. (12) INTERMACS receives no information for patients who receive an investigational device as part of a clinical trial. (12)

As with the original trial, the primary end point was survival at 2 years without reoperation to repair or replace the device or disabling stroke (Rankin scale > 3). Secondary end points were frequency of adverse events, functional status, and quality-of-life assessments.

Table A3 in Appendix 3 summarizes the efficacy results and limitations of the study. Baseline characteristics were similar for the postapproval group and the historical control group. Adverse events in the postapproval group were similar to or lower than those in the historical control group, including improvements in device-related infection (0.22 vs. 0.47) and postoperative bleeding requiring surgery (0.09 vs. 0.23) events per patient-year. Kaplan-Meier survival at 2 years was 62% (postapproval group) versus 58% (historical control group) (*P* = .21).

Table 6 shows a summary of adverse events as reported in Jorde et al. (10) Overall, there were reductions or favourable trends in adverse events between the HC and the PA patients.

Table 6: Adverse Events Reported in Study by Jorde et al

Adverse Events	Historical Control Group (n = 133)		Postapproval Group (n = 247)		*P* Value
	Patients (%)	Event Per Patient Year	Patients (%)	Event Per Patient Year	
Bleeding requiring PRBC	81	1.66	54	0.84	< .001
Bleeding requiring re-exploration	30	0.23	13	0.09	< .001
Infection (local non–device related)	49	0.76	39	0.59	.06
Sepsis	41	0.38	19	0.22	< .001
Device related	35	0.47	19	0.22	< .001
Cardiac arrhythmias	56	0.69	37	0.40	< .001
Renal failure	16	0.10	18	0.15	.12
Right heart failure	23	0.16	18	0.16	.99
RVAD	3.8	0.02	2.4	0.02	.82
Ischemic stroke	8	0.06	4.0	0.03	.09
Hemorrhagic stroke	11	0.07	7.7	0.05	.37
Hemolysis	3.8	0.02	6.5	0.06	.06
Pump thrombosis	3.8	0.02	3.6	0.03	.87
Pump replacement	9.0	0.06	4.0	0.03	.07

Abbreviations: PRBC, packed red blood cells; RVAD, right ventricular assist device.
Source: Jorde et al. (10)

Jorde et al (10) concluded that results in a commercial setting for destination-therapy patients supported the original clinical trial findings in terms of efficacy and risk profile of the HeartMate II LVAD.

Table A4 describes the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profile in detail regarding the use of left ventricular assist devices (LVADs) for destination therapy in patients with end-stage heart failure who are ineligible for heart transplantation.

Conclusions

Only a continuous-flow LVAD is currently licensed by Health Canada for destination therapy. Pulsatile-flow LVADs are not currently licensed by Health Canada for destination therapy. No studies were identified that compared continuous-flow LVADs to optimal medical management. Therefore an indirect comparison was required to compare continuous-flow LVADs to optimal medical management.

For patients with end-stage heart failure who are ineligible for heart transplantation:

- Moderate-quality evidence indicates that treatment with continuous-flow LVADs improves survival compared with drugs.
- Moderate-quality evidence indicates that treatment with continuous-flow LVADs has higher adverse event rates than drugs.
- Low-quality evidence suggests that treatment with continuous-flow LVADs improves quality of life compared with drugs.

ECONOMIC EVIDENCE REVIEW

Objective

The objective of this analysis was to determine the cost utility and cost-effectiveness of LVADs for destination therapy in patients with end-stage heart failure patients who are ineligible for heart transplantation.

Methods

Search Strategy

An economic literature search was performed on February 9, 2015, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, and the Cochrane Library, for studies published from January 1, 2000, to February 9, 2015. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Published between January 1, 2000, and February 9, 2015
- Economic studies/evaluations: cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses
- Economic evaluations reporting incremental cost-effectiveness ratios (ICERs) (i.e., cost per quality-adjusted life-year [QALY]/life-year gained or cost per event avoided)
- Economic studies in patients with end-stage heart failure
- Economic studies reporting on the following interventions/strategies: LVAD, left ventricular assist system, ventricular assist system, HeartWare ventricular assist device, and ventricular assist device

Exclusion Criteria

- Case reports, case series, letters to the editor
- Patients who were eligible for heart transplantation
- Advanced heart-failure patients receiving LVADs for purposes other than destination therapy

Outcomes of Interest

- Cost utility
- Cost-effectiveness

Results

We conducted a search for existing cost-effectiveness and cost-utility analyses of LVADs. The database search yielded 519 citations published between January 1, 2000, and February 9, 2015 (with duplicates removed). Articles were excluded based on information in the title and abstract. Figure 2 summarizes the search results. The full texts of potentially relevant articles were obtained for further assessment.

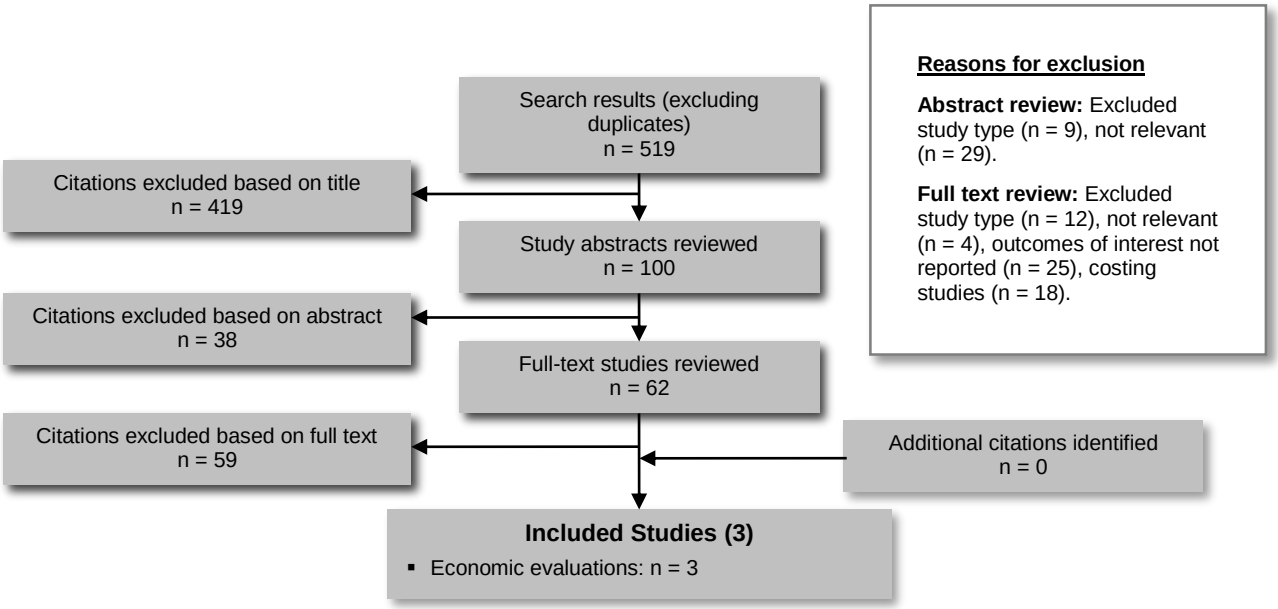

Figure 2: Citation Flow Chart for the Economic Literature Review

Three unique economic evaluations met the inclusion criteria. (26-28) The reference lists of the included studies were hand-searched to identify other relevant studies, but no additional citations were included. Table 7 summarizes the key findings of the included studies.

Long et al (26) found that the average life expectancy for patients who were ineligible for heart transplantation and receiving optimal medical management was 9.4 months with a 1-year survival of 26%—consistent with prior reports. From extrapolation of recent constant hazard rates beyond the first year, the authors found that heart transplant–ineligible patients had a four-fold increase in life expectancy to 4.4 years with destination-therapy LVAD. The predicted survival rates of 78% at 1 year and 62% at 2 years were also consistent with the literature (29) and approximated the rates observed in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry. (22) Destination-therapy LVAD conferred an average life expectancy of 3.6 years among patients aged > 70 years (compared with 4.4 years for 50-year-old patients), with an ICER of $225,000 USD per QALY gained relative to heart transplantation. Destination-therapy LVAD carried an ICER of $202,000 USD per QALY gained or $132,000 USD per life-year gained, compared with optimal medical management. Destination-therapy LVAD substantially improved survival compared with optimal medical management. The authors noted that medical complication rates and/or implantation costs must improve for LVADs to be as cost-effective as other medical technologies.

Neyt et al (27) reported that life expectancy was 0.82 years (95% confidence interval [CI], 0.66–0.99) and 4.33 years (95% CI, 3.17–5.71) for optimal medical management and LVAD, respectively, based on the lifetime model. The discounted incremental effect was 3.23 (95% CI, 2.18–4.49) life-years gained or 2.83 (95% CI, 1.91–3.90) QALYs. Combined with a discounted incremental cost of approximately €299,100 (95% CI, €190,500–€521,000), this resulted in an ICER of €94,100 (95% CI, €59,100–€160,100) per life-year gained or €107,600 (95% CI, €66,700–€181,100) per QALY. Destination-therapy LVAD remained a relatively expensive therapy but led to significantly better survival and quality of life compared with optimal medical management.

Rogers et al (28) found that compared with optimal medical management, continuous-flow LVAD was associated with higher QALYs (1.87 versus 0.37) and life-years gained (2.42 versus 0.64) and significantly higher 5-year costs ($360,407 USD versus $62,856 USD). The ICER for continuous-flow LVAD was $198,184 USD per QALY and $167,208 USD per life-year gained. The authors concluded that the cost-effectiveness of continuous-flow LVADs for destination therapy had improved significantly relative to pulsatile-flow devices. This change was explained by significant improvements in survival and functional status and a reduction in implantation costs.

Table 7: Results of Economic Literature Review for Continuous-Flow LVAD

Name, Year Location	Study Design Perspective Time Horizon	Population Indication	Intervention Comparator	Results			Conclusion
				Health Outcomes	Costs	Cost-Effectiveness	
Long et al, 2014 (26) United States	CEA, decision-analytic model Society Lifetime	INTERMACS for survival LVAD as DT for transplant-ineligible stage D heart failure patients	LVAD as DT, LVAD as BTT, LVAD as BTC for transplantation vs. OMM	Survival, QOL, incremental cost-effectiveness. Net gain of 3.64 LYG 2.38 QALYs	2012 US dollars Discounted incremental cost: $480,400 Discount rate: 3% for costs and QALYs	$131,800 per LYG $201,600 per QALY	Destination-therapy LVAD significantly improved life expectancy in heart transplant–ineligible patients Further reductions in adverse events or improved QOL are needed for DT LVAD to be cost-effective
Neyt et al, 2013 (27) Netherlands	CUA, Markov model Society Lifetime	REMATCH (30): 129 patients 200 (treatment effect), 69 real-world patients for cost; mean age 64; 83% male Adults with chronic end-stage heart failure, contraindications for a heart transplant, LVEF of ≤ 25%, and NYHA class IV for at least 90 days despite OMM *RCT and observational data are combined in this evaluation*	CF LVAD as DT vs. OMM	Survival, functional status, QOL, postoperative complications, or device-related adverse events 3.23 LYG 2.83 QALYs	2010 Euros Discounted incremental cost: €299,100 (95% CI, €190,500–€521,000) Discount rate: 4% for cost, 1.5% for effects	€94,100 per LYG €107,600 per QALY	Although DT LVAD improved survival and QOL, it remains a relatively expensive intervention, which renders the reimbursement of this therapy questionable
Rogers et al, 2012 (28) United States	CEA, Markov model Third-party payer 5 years	REMATCH (30): 61 OMM, 134 CF LVAD (treatment effect) Patients with predominantly NYHA class IV symptoms and an LVEF of ≤ 25% Patients were ineligible for heart transplantation	CF LVAD as DT vs. OMM	Survival, QOL, incremental cost-effectiveness 1.78 LYG 1.5 QALYs	2009 US dollars Costs: CF LVAD $360,407, OMM $62,856 Incremental cost: $297,551 Discount rate: 3% for both cost and effects	$167,208 per LYG $198,184 per QALY	The cost-effectiveness associated with CF LVAD for DT has improved significantly relative to PF LVAD. This is explained by significant improvements in survival, functional status and reduction in implantation costs

Abbreviations: BTC, bridge to candidacy; BTT, bridge to transplant; CEA, cost-effectiveness analysis; CF, continuous-flow; CI, confidence interval; CUA, cost-utility analysis; DT, destination therapy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assistive device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OMM, optimal medical management; PF, pulsatile-flow; QALY, quality-adjusted life-year; QOL, quality of life; LYG, life-year gained ;RCT, randomized controlled trial; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure.

Discussion and Conclusions

The cost-effectiveness associated with destination-therapy LVAD over optimal medical management was relatively high, and the ICERs did not fall under traditional thresholds (e.g., $50,000 or $100,000 per QALY). The high cost-effectiveness ratio was driven by the device cost, surgical procedure costs, and post-implant complication costs.

The published economic evaluations addressed the intervention of interest, but none took a Canadian perspective. Nevertheless, the included cost-utility studies considered similar comparators, settings/perspectives, and treatment regimens: the study conducted in the Netherlands closely mimicked the Ontario context, and the studies conducted in the United States closely aligned with the treatment regimens and comparators in Canada.

The included economic evaluations had major limitations based on perspective and setting, but we did not conduct a primary economic evaluation in the Ontario context. Ontario-specific unit costs and care pathways are similar to those in the Netherlands study and most aspects of the United States studies. As well, the cost of the device, surgical procedure, and post-implant complications would have to be significantly reduced to bring this intervention closer to the traditionally held upper threshold of $100,000 ICER per QALY. Improvement in ICERs can be achieved by refinement in patient selection, reduction in perioperative complications, and coordination for early discharge to transitional services, leading to improvement in the economics of LVAD therapy. (31)

The evaluated studies all came to similar conclusions about the potential economic value of LVAD for destination therapy, concluding that LVAD as destination therapy improved survival and quality of life but remained a relatively expensive intervention. (26-28)

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care to estimate the cost burden of LVAD for destination therapy in 2015 and over the following 4 years (2016 to 2019) under the assumption of limited diffusion. All costs are reported in 2015 Canadian dollars.

Objective

The objective of this analysis was to determine the budget impact for the Ontario Ministry of Health and Long-Term Care of LVADs for destination therapy in end-stage heart failure patients who are ineligible for heart transplantation.

Methods

Affected Population

Patients with advanced heart failure who are ineligible for heart transplantation, have survived for 1 year, and are in functional New York Heart Association (NYHA) class IV are considered the most appropriate candidates for destination-therapy LVAD. (22, 32-34) The incidence of chronic heart failure is age-dependent, ranging from 20 per 1,000 among persons aged 65 to 69 years to more than 80 per 1,000 among persons aged 85 years or older. (1) The National Heart, Lung, and Blood Institute estimates that 5% of patients with heart failure are in functional NYHA class IV. (5) Surveys (3) suggest that 5% to 15% of patients with heart failure have persistent severe symptoms and that the remainder are evenly divided between those with mild and moderately severe symptoms. Advanced heart failure patients have a 1-year survival of 10% to 25%. (32) In Ontario, there were 419,551 incident cases of heart failure between 1997 and 2007, of which 216,190 required admission to hospital and 203,361 were treated as outpatients at the time of initial diagnosis. (35)

The end-stage heart failure population is difficult to estimate, and patients who may benefit from LVAD fall within this population. Instead of using a prevalence-based approach, we based the estimated number of eligible destination-therapy LVAD cases on the number of bridge-to-transplantation implants currently performed per year in the four centres in Ontario; in this scenario, the affected population was derived from expert opinion and current practice among patients in the INTERMACS registry. (22) We estimated the number of potential destination-therapy cases to be funded each year based on a ratio of two destination therapy cases to one bridge-to-transplantation case, as reported by the INTERMACS registry (22) and confirmed by experts from Canada and the United States (personal communications from Dr. Stuart Smith [London, ON], and Dr. Joseph Rogers [United States], June 2, 2015).

In Ontario, 47 adult bridge-to-transplantation cases were funded by the Ministry of Health and Long-Term Care in 2014/15. Using the 2:1 ratio described above, we assumed that in the first year 94 destination-therapy LVADs would be implanted, followed by a 20% increase for each subsequent year. In year 5, destination-therapy LVAD would increase to 195 cases (Table 8). We based assumptions about survival on the INTERMACS registry: 81% in year 1 after implant, 70% in year 2, 59% in year 3, and 48% in year 4 (36) for the base-case scenario.

Table 8: Expected Number of Destination Therapy Procedures, 2015 to 2019, Ontario

Year	Destination Therapy Procedures, n
2015	94
2016	113
2017	135
2018	162
2019	195

Canadian Costs

Table 9 outlines the cost assumptions used in the budget impact analysis. The LVAD implant procedure is covered under Ontario Health Insurance Plan billing code R704 (37) for bridge to transplantation; we assumed that the cost would be the same for destination-therapy LVADs. We calculated yearly hospitalization costs using the reported hospitalization rate per destination-therapy patient in the published literature (2.64 times a year). (27) We based the cost ($9,795 per heart failure hospitalization) (38) on an estimate from the Canadian Institute for Health Information (38). We based early outpatient costs for each year of survival on Quebec data published in 2000, updated to 2015 numbers. (39) We assumed that optimal medical management patients with end-stage heart failure ineligible for heart transplantation and 1-year mortality incurred an average yearly cost of $62,856 USD (28) (approximately $77,032 CAD).

Table 9: Average Costs Per Implant Case in Year 1 and for Each Year of Survival Post-Implant

Cost Parameter	Cost, $	Source
LVAD implantation per case funding	$182,600	Personal communication from Julie Trpkovski, Trillium Gift of Life Network (Toronto, ON), June 2, 2015. Cost is per bridge-to-transplantation case; total cost for device and cost associated with hospitalization cost per surgery
LVAD implantation professional service cost	$2,800	• Schedule of Benefits for Physician Services (37) R704, $2,163 • Assistant fees ($12.04 x 18 units), $216.72 • Anesthetist fees ($15.01 x 28 units), $420.28
Yearly rehospitalization for LVAD	$25,859	2.64 x cost per heart failure hospitalization (28, 38)
Yearly outpatient costs for every year of survival	$18,923	Based on 2000 costs, updated to 2015 (39)
HeartMate II Left Ventricular Assist System and Patient Support Kit	$98,975	Manufacturer price catalogue
Cost per heart failure hospitalization	$9,795	Canadian Institute for Health Information (38)

Abbreviation: LVAD, left ventricular assist device.

For year 1 of the introduction of destination-therapy LVAD, we computed the total cost for eligible patients and subtracted the cost of medical management to determine the net cost. In subsequent years (2016 to 2019), we added the cost of maintaining the total number of surviving patients from previous years to the yearly cost of implants.

Results

Base-Case Analysis

Under the assumptions outlined above, we estimated that adopting destination-therapy LVAD would lead to an overall increase in per-patient costs (Table 10). In the first year, the total cost per eligible case would constitute a net increase over optimal medical management, followed by an additional annual survival maintenance cost for each patient.

Table 10: Net Budget Impact Per Destination-Therapy LVAD Implant Case in Ontario

Implant Case	Net Budget Impact
First year of device implant	**$153,150**
Patient survival cost per year	**$44,782**

Abbreviations: LVAD, left ventricular assist device.

The net overall impact to the Ministry of Health and Long-Term Care would be approximately $13.6 million in year 1 (2015) for the 94 implants. The maintenance cost for the surviving patients and new implant cases in year 5 (2019) would be about $45 million (Table 11).

Table 11: Net Budget Impact of Adopting Destination-Therapy LVAD in Ontario, 2015 to 2019

Year	Net Budget Impact (millions)
2015	**$13.6**
2016	**$20.7**
2017	**$27.8**
2018	**$35.8**
2019	**$45.0**

Abbreviation: LVAD, left ventricular assist device.

Sensitivity Analyses

We found that the budget impact analysis was sensitive to the total number of LVAD procedures that centres can perform each year (Table 12). We varied the number of implants per year at 75% and 50% of the base case, and found a reduction in the total cost to the Ministry of Health and Long-Term Care over the base case.

Table 12: Budget Impact of Adopting Destination-Therapy LVAD in Ontario at 75% and 50% of the Base Case, 2015 to 2019

Year	Net Budget Impact (Millions)	
	75%	50%
2015	**$10.2**	**$6.8**
2016	**$15.5**	**$10.3**
2017	**$20.8**	**$13.9**
2018	**$26.9**	**$17.9**
2019	**$33.7**	**$22.5**

Abbreviation: LVAD, left ventricular assist device.

If complications arose as a result of the LVAD, the number of per-patient rehospitalizations post-implant increased by one visit (Table 13). In the future, if there was a decrease in post-implant adverse events, the number of rehospitalizations decreases and there was a corresponding decrease in costs.

Table 13: Budget Impact of Adopting Destination-Therapy LVAD in Ontario With Change in the Number of Post-Implant Rehospitalizations in the Base Case, 2015 to 2019

Year	Net Budget Impact (Millions)	
	Increased Rehospitalization by 1 Visit	Decreased Rehospitalization by 1 Visit
2015	**$14.3**	**$12.9**
2016	**$22.5**	**$18.8**
2017	**$30.6**	**$24.9**
2018	**$39.8**	**$31.8**
2019	**$50.2**	**$39.8**

Abbreviations: LVAD, left ventricular assist device.

Limitations

- The estimated number of individuals eligible for a destination-therapy LVAD was based on the currently funded volume of bridge-to-transplantation patients in Ontario and estimates of the volume of the most recent INTERMACS data, which suggest a ratio of two destination-therapy LVAD implants for every one bridge-to-transplantation LVAD implant; estimates based on these assumptions may be too generalized and may not reflect the end-stage heart failure patients who will benefit the most.
- We assumed capacity would increase by 20% per annum after the first year; this would depend on the volume of procedures that can be conducted at each implantation centre.
- We assumed that LVAD implantation funding for destination therapy was equivalent to bridge-to-transplantation LVAD implants, which are currently funded by the Ministry of Health and Long-Term Care at $182,600 per case; this figure may be an under- or overestimate of the actual costs associated with a destination-therapy LVAD implant.
- We based yearly outpatient costs on an estimate from a 2000 Quebec evaluation inflated to 2015 dollars; this cost may not reflect treatment patterns, as there have been technological advances in LVAD devices, implantation procedures, and related treatment for these patients both pre- and post-implantation.

Conclusions

- The expected budget impact for the Ministry of Health and Long-Term Care of each destination-therapy LVAD implant would be an average net cost of $153,150 per patient in the year of implantation and an average maintenance cost of $44,782 for each year of survival after that.
- The expected net budget impact to the Ministry of Health and Long-Term Care for destination-therapy LVAD would be $13.6 million in 2015, $20.7 million in 2016, $27.8 million in 2017, $35.8 million in 2018, and $45.0 million in 2019.

LIST OF ABBREVIATIONS

AMSTAR	Assessment of Multiple Systematic Reviews
CI	Confidence interval
CINAHL	Cumulative Index to Nursing & Allied Health Literature
CMS	Center for Medicare and Medicaid Services
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
INTERMACS	Interagency Registry for Mechanically-Assisted Circulatory Support
LVAD	Left ventricular assist device
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial
SF-36	36-item Short Form Health Survey

APPENDICES

Appendix 1: Literature Search Strategies

Clinical Evidence Review

Search date: March 04, 2015
Databases searched: All Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <January 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to January 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2015>, EBM Reviews - Health Technology Assessment <1st Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2015>, Embase <1980 to 2015 Week 09>, All Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
---

1 exp Heart Failure/ (409686)
2 ((end stage* or endstage* or advance* or acute*) adj4 heart adj4 failur*).tw. (31611)
3 Cardiomyopathies/ (62238)
4 cardiomyopath*.tw. (121069)
5 exp Ventricular Dysfunction/ (40907)
6 (ventricul* adj3 dysfunct*).tw. (47405)
7 Shock, Cardiogenic/ (21346)
8 (cardiogenic* adj3 shock*).tw. (19244)
9 Myocarditis/ (28714)
10 (carditis or myocardit*).tw. (29590)
11 or/1-10 (604425)
12 Heart-Assist Devices/ (16083)
13 (((heart or ventric* or vascular*) adj3 assist* adj3 (device* or pump* or system* or treat* or therap* or surg*)) or (artificial adj3 ventricl*)).tw. (19209)
14 Assisted Circulation/ (11246)
15 (assist* adj2 circulat*).tw. (3299)
16 Ventricular Dysfunction, Left/su, th [Surgery, Therapy] (4193)
17 (left ventricl* assist* adj3 (device* or system* or pump*)).tw. (159)
18 (LVAD or LVAS or VAS or HVAD or VAD).tw. (100927)
19 (heartmate or novacor or ventrassist or duraheart or terumo or jarvik 2000 or heartware or coraide or lionheart).tw. (5284)
20 or/12-19 (130268)
21 11 and 20 (22688)
22 exp Animals/ not (exp Animals/ and Humans/) (8076493)
23 21 not 22 (21476)
24 (case reports or congresses).pt. (1775111)
25 23 not 24 (19571)
26 limit 25 to (english language and yr="2012 -Current") [Limit not valid in CDSR,DARE; records were retained] (6039)
27 26 use pmoz,cctr,coch,dare,clhta,cleed (1847)
28 exp heart failure/ (409686)
29 ((end stage* or endstage* or advance* or acute*) adj4 heart adj4 failur*).tw. (31611)
30 cardiomyopathy/ (62231)
31 cardiomyopath*.tw. (121069)
32 heart ventricle function/ (11927)
33 (ventricul* adj3 dysfunct*).tw. (47405)
34 cardiogenic shock/ (21346)
35 (cardiogenic* adj3 shock*).tw. (19244)
36 myocarditis/ (28714)
37 (carditis or myocardit*).tw. (29590)
38 or/28-37 (592191)
39 heart assist device/ (16083)
40 (((heart or ventric* or vascular*) adj3 assist* adj3 (device* or pump* or system* or treat* or therap* or surg*)) or (artificial adj3 ventricl*)).tw. (19209)
41 assisted circulation/ (11246)
42 (assist* adj2 circulat*).tw. (3299)
43 exp left ventricular assist device/ (4501)
44 heart ventricle function/su, th [Surgery, Therapy] (44)
45 (left ventricl* assist* adj3 (device* or system* or pump*)).tw. (159)
46 (LVAD or LVAS or VAS or HVAD or VAD).tw. (100927)
47 (heartmate or novacor or ventrassist or duraheart or terumo or jarvik 2000 or heartware or coraide or lionheart).tw. (5284)
48 or/39-47 (127232)
49 38 and 48 (19374)
50 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38110611)

51 exp humans/ or exp human experimentation/ or exp human experiment/ (29642204)
52 50 not 51 (8494616)
53 49 not 52 (18269)
54 case report/ or conference abstract.pt. (5376355)
55 53 not 54 (11714)
56 limit 55 to english language [Limit not valid in CDSR,DARE; records were retained] (10420)
57 limit 56 to yr="2012 -Current" [Limit not valid in DARE; records were retained] (3172)
58 57 use emez (1768)
59 27 or 58 (3615)
60 remove duplicates from 59 (2560)

Economic Literature Review

Search requested by: Amar Chadee
Search date: February 9, 2015
Librarian: Kaitryn Campbell
Databases searched: All Ovid MEDLINE <1946 to Present>, Embase <1974 to 2015 Feb 06>
Limits: English; 2000-current

Search Strategy:

#	Searches	Results
1	exp Heart Failure/ use prmz	88701
2	((end stage* or endstage* or advance* or acute*) adj4 heart adj4 failur*).tw.	30290
3	Cardiomyopathies/ use prmz	21765
4	Cardiomyopathy/ use oemezd	41993
5	cardiomyopath*.tw.	120225
6	Ventricular Dysfunction/ use prmz	1338
7	Heart Ventricle Function/ use oemezd	11797
8	(ventricul* adj3 dysfunct*).tw.	45598
9	Shock, Cardiogenic/ use prmz	6455
10	Cardiogenic Shock/ use oemezd	15551
11	(cardiogenic* adj3 shock*).tw.	19316
12	Myocarditis/	29334
13	(carditis or myocardit*).tw.	29142
14	or/1-13	345279
15	Heart-Assist Devices/ use prmz	9079
16	Heart Assist Device/ use oemezd	6727
17	(((cardiac* or heart or ventric* or vascular*) adj3 assist* adj3 (device* or pump* or system* or treat* or therap* or surg*)) or (artificial adj3 ventricl*)).tw.	19799
18	Assisted Circulation/ use prmz	3210
19	(assist* adj2 circulat*).tw.	3476
20	exp Ventricular Dysfunction, Left/ use prmz	22617
21	exp Left Ventricular Assist Device/ use oemezd	4437
22	Ventricular Assist Device/ use oemezd	1374
23	(left ventricl* assist* adj3 (device* or system* or pump*)).tw.	159
24	(LVAD or LVAS or VAS or HVAD or VAD or LVADs or LVASs or VASs or HVADs or VADs).tw.	91445
25	(heartmate or novacor or ventrassist or duraheart or terumo or jarvik 2000 or incor or Excor* pediatric or Heartassist or micromed debakey VAD or MTIHeartLVAD or heartware or coraide or lionheart or "HM II").mp.	9295

26	or/15-25	138886
27	(left ventric* assist* adj (device* or system* or pump*)).ti.	6247
28	(14 and 26) or 27	29693
29	*Economics/ use prmz	10383
30	*Economics, Medical/ use prmz	5235
31	*Economics, Pharmaceutical/ use prmz	1324
32	exp "Costs and Cost Analysis"/ use prmz	184496
33	exp Models, Economic/ use prmz	10447
34	Markov Chains/ use prmz	10101
35	Monte Carlo Method/ use prmz	20511
36	Quality-Adjusted Life Years/ use prmz	7269
37	*Economic Aspect/ use oemezd	14096
38	Health Economics/ use oemezd	34180
39	exp Health Care Cost/ use oemezd	213351
40	exp Economic Evaluation/ use oemezd	221302
41	exp Pharmacoeconomics/ use oemezd	171292
42	(econom* or cost or costly or costing or costed or price or prices or pricing or priced or discount or discounts or discounted or discounting or expenditure or expenditures or budget* or afford* or pharmacoeconomic* or pharmaco-economic*).tw.	1234483
43	(cost* adj1 (util* or effective* or efficac* or benefit* or consequence* or analy* or minimi* or saving* or breakdown or lowering or estimate* or variable* or allocation or control or illness or sharing or life or lives or affordabl* or instrument* or technolog* or day* or fee or fees or charge or charges)).tw.	260955
44	(decision adj1 (tree* or analy* or model*)).tw.	25389
45	((value or values or valuation) adj2 (money or monetary or life or lives or costs)).tw.	8496
46	(qoly or qolys or hrqol or qaly or qalys or qale or qales).tw.	35349
47	(sensitivity analys*s or "willingness to pay" or quality-adjusted life year* or quality adjusted life year* or quality-adjusted life expectanc* or quality adjusted life expectanc*).tw.	54413
48	(unit-cost or unit-costs or markov).tw.	32750
49	or/29-48	1738854
50	28 and 49	969
51	(case reports or congresses or conference abstract).pt.	3515820
52	Case report/ use oemezd	1968926
53	50 not (51 or 52)	792
54	limit 53 to english language	728
55	limit 54 to yr="2000 -Current"	602
56	remove duplicates from 55	490

The Cochrane Library

#	Searches	Results
1	MeSH descriptor: [Heart Failure] this term only	5634
2	MeSH descriptor: [Cardiomyopathies] this term only	249
3	MeSH descriptor: [Ventricular Dysfunction] this term only	67
4	MeSH descriptor: [Shock, Cardiogenic] this term only	164
5	MeSH descriptor: [Myocarditis] this term only	85
6	(end stage* or endstage* or advance* or acute*) near/4 heart near/4 failur*:ti,ab,kw or cardiomyopath*:ti,ab,kw or ventricul* near/3 dysfunct*:ti,ab,kw or cardiogenic* near/3 shock*:ti,ab,kw or carditis or myocardit*:ti,ab,kw (Word variations have been searched)	6601
7	#1 or #2 or #3 or #4 or #5 or #6	10764
8	MeSH descriptor: [Heart-Assist Devices] this term only	190
9	MeSH descriptor: [Assisted Circulation] this term only	19
10	MeSH descriptor: [Ventricular Dysfunction, Left] explode all trees	1664
11	((cardiac* or heart or ventric* or vascular*) near/3 assist* near/3 (device* or pump* or system* or treat* or therap* or surg*)) or (artificial near/3 ventricl*):ti,ab,kw or assist* near/2 circulat*:ti,ab,kw or left ventricl* assist* near/3 (device* or system* or pump*):ti,ab,kw or LVAD or LVAS or VAS or HVAD or VAD or LVADs or LVASs or VASs or HVADs or VADs:ti,ab,kw or heartmate or novacor or ventrassist or duraheart or terumo or "jarvik 2000" or incor or "Excor pediatric" or Heartassist or "micromed debakey VAD" or MTIHeartLVAD or heartware or coraide or lionheart or "HM II" (Word variations have been searched)	10200
12	#8 or #9 or #10 or #11	11824
13	left ventric* assist* next (device* or system* or pump*):ti (Word variations have been searched)	74
14	(#7 and #12) or #13 Publication Year from 2000 to 2015, in Technology Assessments and Economic Evaluations	75

Appendix 2: AMSTAR Scores of Included Systematic Reviews

Table A1: AMSTAR Scores

Author, Year	AMSTAR Score	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
NICE, 2014 (6)	7	✓		✓			✓	✓	✓	✓		
Boothroyd et al, 2013 (9)	3	✓	✓							✓		
Rector et al, 2012 (11)	6	✓		✓			✓	✓	✓	✓		

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews; NICE, National Institute for Health and Care Excellence.
[a]Maximum possible score is 11. Details of AMSTAR score are described in Shea et al. (7)

Appendix 3: Study Characteristics

Table A2: Characteristics of Studies in Systematic Review by National Institute for Health and Care Excellence

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr>
<td>Kirklin et al, 2012 (12)</td>
<td>INTERMACS

<u>Inclusion criteria</u>
• ≥ 18 y
• Advanced HF
• Treatment strategy: DT</td>
<td>1,287</td>
<td>2006–2011</td>
<td>2 y</td>
<td>
<u>Survival From Death of Any Cause (Kaplan-Meier Estimates)</u>
<table>
<tr><th rowspan="2">LVAD</th><th colspan="3">% Survival</th></tr>
<tr><th>6 mo</th><th>1 y</th><th>2 y</th></tr>
<tr><td>CF (n = 1,160)</td><td>84</td><td>76</td><td>67</td></tr>
<tr><td>PF (n = 127)</td><td>74</td><td>68</td><td>45</td></tr>
<tr><td>Any type (n = 1,287)</td><td>83</td><td>75</td><td>62</td></tr>
</table>
Between-group difference P < .0001.

<u>Quality-of-Life (EQ-5D Visual Analog Scale) in Patients Treated by CF LVADs</u>
<table>
<tr><th>Test</th><th>Baseline (n = 654)</th><th>3 mo (n = 398)[a]</th><th>6 mo (n = 345)[a]</th><th>1 y (n = 186)[a]</th></tr>
<tr><td>EQ-5D Visual Analog Scale[b]</td><td>45</td><td>72</td><td>75</td><td>72</td></tr>
</table>
[a]Significant improvements from baseline observed at all follow-up assessments (P < .05).
[b]EQ-5D scores range from 0 to 100; higher scores indicate better quality of life.

<u>Adverse Events in First 12 Months for DT Patients</u>
<table>
<tr><th rowspan="2">Adverse Event</th><th colspan="2">PF (n=127)</th><th colspan="2">CF (n=1160)</th><th rowspan="2">Hazard Ratio (PF Rate/CF Rate)</th><th rowspan="2">P Value</th></tr>
<tr><th>Number of events (n)</th><th>Rate (events/100 patient months)</th><th>Number of events (n)</th><th>Rate (events/100 patient months)</th></tr>
<tr><td>Device malfunction</td><td>38</td><td>3.69</td><td>100</td><td>1.15</td><td>3.21</td><td>< .0001</td></tr>
<tr><td>Bleeding</td><td>150</td><td>14.56</td><td>1040</td><td>11.94</td><td>1.22</td><td>.008</td></tr>
<tr><td>Infection</td><td>236</td><td>22.91</td><td>705</td><td>8.09</td><td>2.83</td><td>< .0001</td></tr>
<tr><td>Neurologic dysfunction</td><td>30</td><td>2.91</td><td>162</td><td>1.86</td><td>1.57</td><td>.006</td></tr>
<tr><td>Renal dysfunction</td><td>30</td><td>2.91</td><td>141</td><td>1.62</td><td>1.80</td><td>< .0001</td></tr>
<tr><td>Hepatic dysfunction</td><td>7</td><td>0.68</td><td>50</td><td>0.57</td><td>1.18</td><td>.24</td></tr>
<tr><td>Respiratory failure</td><td>41</td><td>3.98</td><td>230</td><td>2.64</td><td>1.51</td><td>.004</td></tr>
<tr><td>Wound dehiscence</td><td>10</td><td>0.97</td><td>19</td><td>0.22</td><td>4.45</td><td>< .0001</td></tr>
</table>
</td>
<td>
• Not randomized: registry of patients who receive LVADs (no control group); therefore there could be unmeasured or unknown confounding factors
• Baseline characteristics/similarities of patients not reported
• Patients enter registry over different periods
• Not blinded
• Adverse events reported by treating physicians, not adjudicated by clinical events committee
• Authors state that, among 1,287 DT patients, follow-up was available for > 99% of patients at follow-up date of December 31, 2011
• All patients are followed as part of requirements of INTERMACS until 1 of 3 end points is reached: death, transplant, or device explant for recovery
• 31 of 1,287 patients were treated by biventricular assist devices and were included in analysis
• Subgroup analyses performed for continuous-flow vs. pulsatile-flow LVADs
</td>
</tr>
</table>

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Psychiatric episode</td><td>21</td><td>2.04</td><td>78</td><td>0.90</td><td>2.28</td><td>< .0001</td></tr>
<tr><td>Right HF</td><td>14</td><td>1.36</td><td>151</td><td>1.73</td><td>0.78</td><td>.75</td></tr>
<tr><td>MI</td><td>0</td><td>0.00</td><td>3</td><td>0.03</td><td>-</td><td>-</td></tr>
<tr><td>Cardiac arrhythmia</td><td>55</td><td>5.34</td><td>339</td><td>3.89</td><td>1.37</td><td>.009</td></tr>
<tr><td>Pericardial drainage</td><td>10</td><td>0.97</td><td>54</td><td>0.62</td><td>1.57</td><td>.06</td></tr>
<tr><td>Arterial non-CNS thrombosis</td><td>5</td><td>0.49</td><td>17</td><td>0.20</td><td>2.49</td><td>.01</td></tr>
<tr><td>Venous thrombosis</td><td>11</td><td>1.07</td><td>56</td><td>0.64</td><td>1.66</td><td>.03</td></tr>
<tr><td>Hemolysis</td><td>0</td><td>0.00</td><td>55</td><td>0.63</td><td>-</td><td>-</td></tr>
<tr><td>All adverse events</td><td>685</td><td>66.50</td><td>3,273</td><td>37.56</td><td>1.77</td><td>< .0001</td></tr>
</table>
</td><td></td></tr>
<tr><td>Slaughter et al,
2009 (13)</td><td>RCT (HeartMate II [CF] vs. HeartMate XVE [PF])

PF device not currently licensed by Health Canada

Inclusion criteria
• ≥ 18 y of age
• Body surface area ≥ 1.5 m^2
• Advanced HF ineligible for heart transplantation
• HF refractory to OMM
• NYHA Class IIIB or IV HF for at least 45 of 60 days before enrolment or dependence on an intra-aortic balloon pump for period of 7 d or inotropes for 14 d before enrolment
• LVEF ≤ 25%
• Peak oxygen consumption ≤ 14 mL/kg/min or < 50% of predicted value

Exclusion criteria
• HF caused by or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, active myocarditis, or restrictive cardiomyopathy.</td><td>200
(134 CF LVAD vs. 66 PF LVAD)</td><td>2005–2007</td><td>Unclear</td><td>The as-treated analysis consisted of 133 CF LVAD patients and 59 PF LVAD patients

Median duration of support was 1.7 y (range 0.0–3.7) for CF LVADs and 0.6 y (range 0.0–2.1) for PF LVAD patients

Primary End Point
<table>
<tr><th>End Point</th><th>CF Patients (N = 134)
n (%)</th><th>PF Patients (N = 166)
n (%)</th><th>P Value</th></tr>
<tr><td>Survival free from disabling stroke and reoperation to repair or replace LVAD at 2 y</td><td>62 (46)</td><td>7 (11)</td><td>< .001</td></tr>
<tr><td colspan="4">First event that prevented patient from reaching primary end point</td></tr>
<tr><td>Stroke (ranking score > 3)</td><td>15 (11)</td><td>8 (12)</td><td>.56</td></tr>
<tr><td>Reoperation (repair or replace pump)</td><td>13 (10)</td><td>24 (24)</td><td>< .001</td></tr>
<tr><td>Death within 2 y of implantation</td><td>44 (33)</td><td>27 (41)</td><td>.048</td></tr>
<tr><td>Any</td><td>72 (54)</td><td>59 (89)</td><td><.001</td></tr>
</table>
The as-treated analysis showed survival was significantly better for patients with CF LVADs than for those with PF LVADs (relative risk, 0.54; 95% CI 0.34–0.86; P = .008). 1- and 2-year survival rates were 68% (95% CI 60–76) and 58% (95% CI 49–67), respectively, with CF LVADs and 55% (95% CI 42–69) and 24% (95% CI 1–46) with PF LVADs (as-treated analysis)

Functional status and quality of life reported for as-treated analysis indicated improvement according to time since device implant</td><td>• Study sponsored by manufacturers
• Data collected by study coordinators at participating centres and analyzed and audited by manufacturers
• Intention-to-treat analysis of primary outcome; other outcomes analyzed as treated
• Impossible to ensure that patients and investigators were unaware of treatment assignments. Potential for bias regarding patient-reported outcomes, such as functional abilities and quality of life
• Most centres had more experience with PF LVADs than with CF LVADs.
• Postoperative medical care was managed according to each investigator's preference and usual practice
• Subsequent to randomization, 8 patients were not implanted with a device and 4 patients were implanted with a device outside their randomization assignment
• Definitions of NYHA Class IIIB or Class IV HF were not included in</td></tr>
</table>

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr>
<td></td>
<td>

Technical obstacles pose high surgical risk in judgment of investigator
Existence of any ongoing mechanical circulatory support other than intra-aortic balloon counterpulsation
BMI > 40 kg/m^2
Positive pregnancy test
Presence of mechanical aortic valve that will not be converted to bioprosthesis at time of LVAD implant
History of cardiac transplant or cardiomyoplasty
Platelet count ≤ 50,000
Evidence of untreated aortic aneurysm ≥ 5 cm
Psychiatric disease, irreversible cognitive dysfunction, or psychosocial issue that are likely to impair compliance with study protocol and LVAD management
Active uncontrolled infection
Intolerance to anticoagulant or antiplatelet therapies or any other perioperative or postoperative therapy the investigator will require based upon patient's health status
INR ≥2.5, which is not due to anticoagulant therapy within 5 days
Evidence of intrinsic hepatic disease as defined by liver enzyme values that are > 5 times the upper limit of normal or biopsy proven liver cirrhosis
History of severe COPD or severe restrictive lung disease
Fixed pulmonary hypertension with a PVR ≥8 Wood units that is unresponsive to pharmacologic intervention
History of stroke within 90 days prior to enrolment or a history of cerebral vascular disease with significant (80%) extra cranial stenosis
Serum creatinine ≥3.5 mg/dl or the need for chronic renal

</td>
<td></td>
<td></td>
<td></td>
<td>
<u>6-Minute Walking Test Distances</u>
<table>
<tr><th rowspan="2">Group</th><th colspan="2">Walking Distance (Mean±SD)</th><th rowspan="2">P Value for Treatment Over Time</th><th rowspan="2">P Value Between Treatments at 12 Mo[a]</th></tr>
<tr><th>Baseline, m</th><th>1 Y, m</th></tr>
<tr><td>CF</td><td>182 ± 140 (n = 50)</td><td>318 ± 164 (n = 61)</td><td>< .001</td><td rowspan="2">.62</td></tr>
<tr><td>PF</td><td>172 ± 108 (n = 19)</td><td>306 ± 145 (n = 12)</td><td>< .001</td></tr>
</table>
[a]No significant difference observed between groups at 1-year follow-up (P = .22).

<u>Quality-of-Life Scores</u>
MLWHF Questionnaire: scores range from 0 to 105; lower scores indicate better quality of life
KCCQ: scores range from 0 to 100; higher scores indicate better quality of life
<table>
<tr><th>Outcome</th><th>Group</th><th>Baseline (Mean ± SD)</th><th>1 Y (Mean ± SD)</th><th>P Value for Treatment Over Time</th><th>P Value Between Treatments at 12 Mo</th></tr>
<tr><td rowspan="2">MLWHF score[a]</td><td>CF</td><td>75.4 ± 17.7 (n = 116)</td><td>34.1 ± 22.4 (n = 76)</td><td>< .001</td><td rowspan="2">.03</td></tr>
<tr><td>PF</td><td>76.1 ± 18.0 (n = 49)</td><td>44.4 ± 23.2 (n = 19)</td><td>< .001</td></tr>
<tr><td rowspan="2">KCCQ clinical summary score[b]</td><td>CF</td><td>35.1 ± 18.5 (n = 115)</td><td>68.6 ± 21.8 (n = 76)</td><td>< .001</td><td rowspan="2">.06</td></tr>
<tr><td>PF</td><td>31.6 ± 18.4 (n = 47)</td><td>60.8 ± 20.2 (n = 18)</td><td>< .001</td></tr>
<tr><td rowspan="2">Overall KCCQ score[b]</td><td>CF</td><td>27.4 ± 16.3 (n = 115)</td><td>65.9 ± 20.0 (n = 76)</td><td>< .001</td><td rowspan="2">.12</td></tr>
<tr><td>PF</td><td>46.5 ± 17.4 (n = 47)</td><td>59.1 ± 20.3 (n = 18)</td><td>< .001</td></tr>
</table>
[a]Significant difference observed between groups at 1-year follow-up (P = .03).
[b]No significant difference observed between groups at 1-year follow-up (P = .06).

<u>Adverse Events</u>
<table>
<tr><th>Adverse Event</th><th>CF Patients (N = 133) Number of patients, n (%)</th><th>PF Patients (N = 59) Number of patients, n (%)</th><th>Risk Ratio (95% CI)</th><th>P Value for Interaction</th></tr>
<tr><td>Pump replacement</td><td>12 (9)</td><td>20 (34)</td><td>0.12 (0.06 to 0.26)</td><td><0.001</td></tr>
<tr><td>Ischemic stroke</td><td>11 (8)</td><td>4 (7)</td><td>0.59 (0.18 to 1.92)</td><td>0.38</td></tr>
</table>
</td>
<td>
published study or supplemental material.

Among 181 patients assessed for NYHA class at baseline, 5 were Class IIIA (undefined in study), 38 were Class IIIB, and 138 were Class IV. Neither published study nor published supplement accompanying it gave any breakdown by NYHA class of patient characteristics or outcomes

</td>
</tr>
</table>

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr><td></td><td>replacement therapy (e.g., chronic dialysis)
• Significant peripheral vascular disease accompanied by rest pain or extremity ulceration
• Patient has moderate to severe aortic insufficiency without plans for correction during pump implantation surgery
• Patient receiving calcium channel blocker (except amlodipine) or a Type 1 or Type III antiarrhythmic (except amiodarone) within 28 days prior to enrolment
• Any condition, other than HF that could limit survival to less than 3 years

Intent to treat principle used for primary outcome measure (CF versus PF). Analyses of secondary outcome measures conducted using as-treated principle.

Primary composite endpoint was 2 years post-implant survival, free of stroke resulting in a Modified Rankin Score >3 or reoperation to repair or replace the device. Modified Rankin Score is a functional assessment that ranges from 0 (no symptoms) to 6 (dead).</td><td></td><td></td><td></td><td>
<table>
<tr><td>Hemorrhagic stroke</td><td>15 (11)</td><td>5 (8)</td><td>0.59 (0.20 to 1.71)</td><td>0.33</td></tr>
<tr><td>LVAD related infection</td><td>47 (35)</td><td>21 (36)</td><td>0.53 (0.32 to 0.88)</td><td>0.01</td></tr>
<tr><td>Local nonLVAD infection</td><td>65 (49)</td><td>27 (46)</td><td>0.57 (0.36 to 0.90)</td><td>0.02</td></tr>
<tr><td>Sepsis</td><td>48 (36)</td><td>26 (44)</td><td>0.35 (0.21 to 0.57)</td><td><0.001</td></tr>
<tr><td>Bleeding requiring packed red cells</td><td>108 (81)</td><td>45 (76)</td><td>0.68 (0.46 to 1.02)</td><td>0.06</td></tr>
<tr><td>Bleeding requiring surgery</td><td>40 (30)</td><td>9 (15)</td><td>0.80 (0.39 to 1.64)</td><td>0.57</td></tr>
<tr><td>Right HF managed with extended use of inotropes</td><td>27 (20)</td><td>16 (27)</td><td>0.30 (0.15 to 0.59)</td><td><0.001</td></tr>
<tr><td>Right HF managed with RVAD</td><td>5 (4)</td><td>3 (5)</td><td>0.33 (0.08 to 1.43)</td><td>0.12</td></tr>
<tr><td>Cardiac arrhythmia</td><td>75 (56)</td><td>35 (59)</td><td>0.53 (0.33 to 0.83)</td><td>0.006</td></tr>
<tr><td>Respiratory failure</td><td>50 (38)</td><td>24 (41)</td><td>0.39 (0.23 to 0.66)</td><td><0.001</td></tr>
<tr><td>Renal failure</td><td>21 (16)</td><td>14 (24)</td><td>0.30 (0.14 to 0.63)</td><td><0.001</td></tr>
<tr><td>LVAD thrombosis</td><td>5 (4)</td><td>0</td><td>-</td><td>NR</td></tr>
<tr><td>Rehospitalization*</td><td>107 (94)</td><td>42 (96)</td><td>0.62 (0.41 to 0.93)</td><td>0.02</td></tr>
</table>
*Reasons for rehospitalisation not reported
</td><td></td></tr>
<tr><td>Park et al, 2012 (15)</td><td>Case series; continuation of Slaughter et al, 2009

Inclusion criteria
• Advanced HF ineligible for heart transplantation
• HF refractory to OMM
• NYHA Class IIIB or IV HF for at least 45 of 60 days before enrolment or dependence on intra-aortic balloon pump for 7 d or inotropes for 14 d before enrolment
• LVEF < 25%
• Peak oxygen consumption < 14 mL/kg/min

All patients treated by CF</td><td>414</td><td>Early trial 2005–2007; 133 patients.
Late trial 2007–2009; 281 patients</td><td>Minimum 2 y</td><td>Survival curves at 12 and 24 mo for late group were 73 ± 3% and 63 ± 3% compared with early trial group of 68 ± 4% and 58 ± 4%, respectively (P = .21 log-rank test).

<u>6-Minute Walking Test Distances</u>
<table>
<tr><th rowspan="2">Group</th><th colspan="2">Walking Distance, m (Mean±SD)[a]</th><th rowspan="2">P Value Over Time[b]</th></tr>
<tr><th>Baseline</th><th>2 Y</th></tr>
<tr><td>Early</td><td>181 ± 138 (n = 52)</td><td>350 (n = 44)</td><td>< .001</td></tr>
<tr><td>Late</td><td>225 ± 142 (n = 98)</td><td>350 (n = 90)</td><td>< .001</td></tr>
</table>
[a]Results obtained from a graph.
[b]No significant difference observed between groups at 2-y follow-up (P = .907).

<u>Quality-of-Life Scores*</u></td><td>Authors stated in methods section that study was supervised and monitored by manufacturers

Retrospective subanalysis of patients who received CF LVAD (PF LVAD was not included)

Withdrawals not explained or reported.</td></tr>
</table>

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr><td></td><td>Early trial patients were compared with late trial patients to establish whether increasing clinical experience using CF LVADs resulted in better clinical outcomes

Postoperative medical care (including inotropic, antiarrhythmic, anticoagulant and HF therapy) was managed according to each investigator's preference and usual practice</td><td></td><td></td><td></td><td>
MLWHF Questionnaire: scores range from 0 to 105; lower scores indicate better quality of life.
KCCQ: scores range from 0 to 100; higher scores indicate better quality of life.
<table>
<tr><th>Outcome</th><th>Group</th><th>Baseline, Mean ± SD (n)</th><th>2 Y, Mean ± SD (n)</th><th>P Value Over Time</th></tr>
<tr><td rowspan="2">MLWHF score[a,b]</td><td>Early</td><td>66 (116)*</td><td>32 (53)*</td><td>< .001</td></tr>
<tr><td>Late</td><td>65 (250)*</td><td>31 (108)*</td><td>< .001</td></tr>
<tr><td rowspan="2">KCCQ score[b,c]</td><td>Early</td><td>27 ± 16 (115)</td><td>68 (56)*</td><td>< .001</td></tr>
<tr><td>Late</td><td>28 ± 16 (245)</td><td>68 (114)*</td><td>< .001</td></tr>
</table>
[a]Significant difference observed between groups at 2-y follow-up (P = .04).
[b]NICE (6) determined results from a graph in paper by Park et al. (15)
[c]No significant difference observed between groups at 2-year follow-up (P = .08).
*Standard deviation (SD) was not reported for these values.

<u>Adverse Events</u>
<table>
<tr><th>Adverse Event</th><th>Early Patients: N = 133 n (%)</th><th>Late Patients: N = 281 n (%)</th><th>All Patients: N = 414[a] n (%)</th></tr>
<tr><td>Bleeding requiring packed blood cells</td><td>108 (81)</td><td>207 (74)</td><td>315 (76)</td></tr>
<tr><td>Bleeding requiring re-exploration</td><td>40 (30)</td><td>55 (20)</td><td>95 (23)</td></tr>
<tr><td>Local non-LVAD infection</td><td>65 (49)</td><td>126 (45)</td><td>191 (46)</td></tr>
<tr><td>Sepsis</td><td>48 (41)</td><td>78 (28)</td><td>126 (30)</td></tr>
<tr><td>LVAD-related infection</td><td>47 (35)</td><td>84 (30)</td><td>131 (32)</td></tr>
<tr><td>Driveline infection</td><td>42 (32)</td><td>75 (27)</td><td>117 (28)</td></tr>
<tr><td>Pocket infection</td><td>12 (9)</td><td>20 (7)</td><td>32 (8)</td></tr>
<tr><td>Cardiac arrhythmia</td><td>75 (56)</td><td>141 (50)</td><td>216 (32)</td></tr>
<tr><td>Renal failure</td><td>21 (16)</td><td>30 (11)</td><td>51 (12)</td></tr>
<tr><td>Right HF (including extended inotropic support)</td><td>31 (23)</td><td>58 (21)</td><td>89 (21)</td></tr>
<tr><td>RVAD</td><td>5 (4)</td><td>17 (6)</td><td>22 (5)</td></tr>
<tr><td>Ischemic stroke</td><td>11 (8)</td><td>22 (8)</td><td>33 (8)</td></tr>
<tr><td>Hemorrhagic stroke</td><td>15 (11)</td><td>13 (5)</td><td>28 (7)</td></tr>
<tr><td>Pump replacement</td><td>12 (9)</td><td>22 (8)</td><td>34 (8)</td></tr>
<tr><td>Pump thrombosis</td><td>5 (4)</td><td>16 (6)</td><td>21 (5)</td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>[a]All patients with adverse events calculated by NICE (not included in original report).

<u>Cause of Death as Categorized by Authors (Proportion of All Patients)</u>
<table>
<tr><th>Cause of Death</th><th>Early Patients: N = 133
n (%)</th><th>Late Patients: N = 281
n (%)</th><th>All Patients: N = 414
n (%)</th></tr>
<tr><td>Haemorrhagic stroke</td><td>10 (8)</td><td>6 (2)</td><td>16 (4)</td></tr>
<tr><td>Ischaemic stroke</td><td>1 (1)</td><td>9 (3)</td><td>10 (2)</td></tr>
<tr><td>Right heart failure</td><td>5 (4)</td><td>12 (4)</td><td>17 (4)</td></tr>
<tr><td>Bleeding</td><td>4 (3)</td><td>10 (4)</td><td>14 (3)</td></tr>
<tr><td>Sepsis</td><td>5 (4)</td><td>8 (3)</td><td>13 (3)</td></tr>
<tr><td>Multiple organ failure</td><td>2 (2)</td><td>5 (2)</td><td>7 (2)</td></tr>
<tr><td>Loss of power to external components</td><td>4 (3)</td><td>5 (2)</td><td>9 (2)</td></tr>
<tr><td>“Internal components 6 thrombosis; 2 cable” [a]</td><td>3 (2)</td><td>7 (2)</td><td>10 (2)</td></tr>
<tr><td>Other Deaths[b]</td><td>18 (14)</td><td>36 (13)</td><td>54 (13)</td></tr>
</table>
All deaths calculated by NICE (not included in original report).

[a] Very unclear, however cause of death is written as stated by the author.
[b] Other deaths include embolism, anoxic brain injury, traumatic brain injury, cardiac arrest, cardiac failure, heart failure, respiratory failure, pneumonia, amyloidosis, cancer, liver failure, pancreatitis, withdrawal of support, ruptured bladder, subdural haematoma and unknown.</td><td></td></tr>
<tr><td>Rogers et al, 2010 (17)</td><td>Observational comparative study including both DT and BTT patients

Study included patients from RCT by Slaughter et al, 2009

<u>DT Inclusion Criteria</u>
• Patients with NYHA Class IIIB or IV HF ineligible for heart transplantation
• HF refractory to OMM

<u>BTT Inclusion Criteria</u>
• Patients with Class IV HF who were listed as high priority for heart transplantation

All patients treated with CF LVADs</td><td>655 (374 DT vs. 281 BTT)</td><td>2005–2009</td><td>DT: 2 y

BTT: 6 mo</td><td>Significant improvement in NYHA class was observed at 6-mo follow-up (P < .001).

<u>6-Minute Walking Test Distances</u>
<table>
<tr><th>Group</th><th>Baseline, m(Mean ± SD)</th><th>6 Mo, m[a] (Mean ± SD)</th><th>2 Y, m[b] (Mean ± SD)</th></tr>
<tr><td>DT</td><td>204 ± 150</td><td>350 ± 198</td><td>360 ± 210</td></tr>
</table>
[a]Significant improvements observed at 6-month follow-up (P value < .05).
[b] No P values reported

<u>Change in Quality-of-Life Scores</u>
<table>
<tr><th>Outcome</th><th>Group</th><th>6 Mo[a] (Mean change ± SD)</th><th>2 Y[b] (Mean change ± SD)</th></tr>
<tr><td>MLWHF score</td><td>DT</td><td>−39 ± 27</td><td>−41 ± 25</td></tr>
<tr><td>KCCQ clinical summary score</td><td>DT</td><td>37 ± 25</td><td>38 ± 26</td></tr>
<tr><td>Overall KCCQ score[b]</td><td>DT</td><td>39 ± 24</td><td>42 ± 23</td></tr>
</table>
[a]Significant improvement observed at 6-month follow-up (P < .05).
[b]No P value reported.</td><td>Study includes patients from study by Slaughter et al(13)

Treatment groups included patients with different disease severities
• DT patients had higher systolic blood pressure and worse renal function than BTT patients
• BTT patients were younger and more likely to be treated with intravenous inotropic agents or an intra-aortic balloon pump at enrolment

Number of patients varies with each outcome measure</td></tr>
</table>

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Clinically meaningful improvement in KCCQ scores (> 5-point improvement) was reported in 92% of DT patients

<u>Adverse Events</u>
Authors did not report if adverse events were monitored</td><td></td></tr>
<tr><td>Rose et al, 2001 (14)</td><td>RCT (REMATCH Trial)

<u>Inclusion criteria</u>
• Advanced HF ineligible for heart transplantation
• NYHA Class IV HF for ≥ 90 d despite therapy with ACE inhibitors, diuretics, and digoxin
• LVEF < 25%
• Peak oxygen consumption < 12 mL/kg/min
• Continuous need for intravenous inotropic therapy for symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion

<u>DT patients</u>
• Treated by PF LVAD
• Device implanted into a pre-peritoneal pocket or peritoneal cavity, depending on surgeon's preference

<u>OMM patients</u>
• Treatment administered according to guidelines developed by medical committee; involved use of ACE inhibitors and encouraged discontinuation of intravenous inotropic infusions

Primary end point was death from any cause. Trial designed to enroll 140 patients and to continue until 92 deaths had occurred</td><td>129

(68 DT vs. 61 OMM)</td><td>1998–2001</td><td>2 y</td><td>Analyses used intent-to-treat principle. However, numbers analyzed varied by outcome measure

2 patients withdrew from OMM at 1 and 6 mo after enrolment.

<u>Survival (Kaplan-Meier Survival Estimates) (Primary End Point)</u>
<u>Risk of Death From Any Cause:</u>
Relative risk, 0.52; 95% CI 0.34–0.78; P = .001

<u>Median survival:</u>
DT = 408 d
OMM = 150 d (no P value reported)
<u>Survival rate at 1-y follow-up:</u>
DT = 52%
OMM = 25% (P = .002)
<u>Survival rate at 2-y follow-up:</u>
DT = 23%
OMM = 8% (P = .09)
<u>Survival rate for patients < 60 y at 1-y follow-up:</u>
DT = 74%
OMM = 33% (P = .05).
<u>Survival rate for patients between 60 and 69 y at 1-y follow-up:</u>
DT= 47%
OMM = 15% (P = .009)
<u>Survival rate at study close (time not reported):</u>
DT = 39.7% (27/68)
OMM = 11.5% (7/61)

<u>Quality-of-Life and Functional Activity Scores</u>

MLWHF Questionnaire: scores range from 0 to 105; lower scores indicate better quality of life.
SF-36 Health Survey: scores for individual domains range from 0 to 100; higher scores indicate better quality of life.
Beck Depression Inventory: Scores range from 0 to 64; lower scores indicate less severe depression.

<table>
<tr><th>Outcome</th><th>Group</th><th>Baseline, Mean ± SD or Median</th><th>1 Y, Mean ± SD or Median</th></tr>
<tr><td>SF-36 Physical function score[a]</td><td>DT</td><td>19 ± 19</td><td>46 ± 19 (23 of 24 patients assessed)</td></tr>
<tr><td></td><td>OMM</td><td>18 ± 18</td><td>21 ± 21</td></tr>
</table>
</td><td>LVAD was PF device not currently licensed by Health Canada

Patients could continue beta-blockers if they had been administered for ≥ 60 d before enrolment

Patient selection criteria expanded 18 mo after enrolment to include patients with NYHA Class IV heart failure for ≥ 60 d who had peak oxygen consumption ≤ 14 mL/kg/min or patients with NYHA Class IIIB or IV heart failure for ≥ 28 d who had ≤ 14 d of support by intra-aortic balloon pump or who were dependent on intravenous inotropic agents

Two patients in OMM group withdrew from trial 1 and 6 mo after randomization</td></tr>
</table>

Author, Year	Study Design and Methods	Number of Patients	Recruitment Period	Follow-up	Results	Limitations/ Comments

			(6 of 11 patients assessed)
SF36 Emotional role score[a]	DT	33 ± 42	64 ± 45 (23 of 24 patients assessed)
	OMM	25 ± 48	17 ± 28 (6 of 11 patients assessed)
MLWHF score[b]	DT	75 ± 18	41 ± 22 (23 of 24 patients assessed)
	OMM	75 ± 17	58 ± 21 (6 of 11 patients assessed)
Beck Depression Inventory score[a]	DT	19 ± 9	8 ± 7 (22 of 24 patients assessed)
	OMM	16 ± 8	13 ± 7 (5 of 11 patients assessed)
NYHA Class[a]	DT	IV	II(24 of 24 patients assessed)
	OMM	IV	IV (7 of 11 patients assessed)

[a]Significant differences observed between groups at 1-y follow-up ($P < .05$).
[b]No significant difference observed between groups at 1-y follow-up ($P = .11$).

All patients completed baseline testing.

Incidence of serious adverse events as categorised by the authors

Event	DT (N=67) (Rate/ Patient Year)	OMM (N=60) (Rate/ Patient Year)	Rate Ratio (95% CI)
All adverse events	6.45	2.75	2.35 (1.86-2.95)
Non-neurologic bleeding	0.56	0.06	9.47 (2.30-38.90)
Neurologic dysfunction	0.39	0.09	4.35 (1.31-14.50)
Supraventricular arrhythmia	0.12	0.03	3.92 (0.47-32.4)
Peripheral embolic event	0.14	0.06	2.29 (0.48-10.80)
Sepsis	0.60	0.30	2.03 (0.99-4.13)
Local infection	0.39	0.24	1.63 (0.72-3.70)
Renal failure	0.25	0.18	1.42 (0.54-3.71)

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Syncope</td><td>0.04</td><td>0.03</td><td>1.31 (0.12-14.40)</td></tr>
<tr><td>Cardiac arrest</td><td>0.12</td><td>0.18</td><td>0.65 (0.21-2.00)</td></tr>
<tr><td>Non-perioperative MI</td><td>0.02</td><td>0.03</td><td>0.65 (0.04-10.30)</td></tr>
<tr><td>Ventricular arrhythmia</td><td>0.25</td><td>0.56</td><td>0.45 (0.22-0.90)</td></tr>
<tr><td colspan="4">Events related to LVAD</td></tr>
<tr><td>Suspected malfunction of LVAD</td><td>0.75</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Perioperative bleeding</td><td>0.46</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Infection of drive line tract or pocket</td><td>0.41</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Infection of pump interior, inflow tract or outflow tract</td><td>0.23</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Right heart failure</td><td>0.17</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Failure of LVAD</td><td>0.08</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Thrombosis in LVAD</td><td>0.06</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Perioperative MI</td><td>0.00</td><td>N/A</td><td>N/A</td></tr>
</table>
<u>Cause of death as categorised by the authors</u>
<table>
<tr><th>Cause of Death</th><th>DT
(Number of patients)</th><th>OMM
(Number of patients)</th></tr>
<tr><td>LV dysfunction</td><td>1</td><td>50</td></tr>
<tr><td>Sepsis</td><td>17</td><td>1</td></tr>
<tr><td>LVAD failure</td><td>7</td><td>0</td></tr>
<tr><td>Miscellaneous noncardiovascular causes</td><td>5</td><td>0</td></tr>
<tr><td>Cerebrovascular disease</td><td>4</td><td>0</td></tr>
<tr><td>Miscellaneous cardiovascular causes</td><td>2</td><td>1</td></tr>
<tr><td>Pulmonary embolism</td><td>2</td><td>0</td></tr>
<tr><td>Acute MI</td><td>0</td><td>1</td></tr>
<tr><td>Cardiac procedure</td><td>0</td><td>1</td></tr>
<tr><td>Preoperative bleeding</td><td>1</td><td>0</td></tr>
<tr><td>Unknown</td><td>2</td><td>0</td></tr>
</table>
</td><td></td></tr>
<tr><td>Park et al, 2005 (16)</td><td>Longer follow-up of Rose et al

RCT (REMATCH Trial)

<u>Inclusion criteria</u>
• Advanced HF ineligible for heart transplantation</td><td>129

68 DT
61 OMM</td><td>NR</td><td>Up to 4 y</td><td>2 patients withdrew from OMM at 1 and 6 mo after enrolment

Number of patients analyzed: 129 (68 DT vs. 61 OMM); however, numbers analyzed varied by outcome measure.

<u>Survival (Kaplan-Meier Survival Estimates)</u>
<u>Median survival:</u>
DT = 408 d</td><td>Authors stated that limitations to study included:
• Post-hoc analysis of changes in survival over time
• Limited sample size in subgroup analyses affects ability to make adequately powered comparisons</td></tr>
</table>

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr><td></td><td>
• NYHA Class IV HF for ≥ 90 days despite therapy with ACE inhibitors, diuretics, and digoxin
• LVEF < 25%
• Peak oxygen consumption < 12 mL/kg/min
• Continuous need for intravenous inotropic therapy for symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion

Subsequent inclusion criteria allowed for patients with NYHA Class IIIB HF who were taking inotropes for 14 of 28 d before enrolment with intra-aortic balloon pumps.

<u>DT patients</u>
• Treated by PF LVAD
• Device implanted into a pre-peritoneal pocket or peritoneal cavity, depending on surgeon's preference

<u>OMM patients</u>
• Treatment administered according to guidelines developed by medical committee; involved use of ACE inhibitors and encouraged discontinuation of intravenous inotropic infusions
</td><td></td><td></td><td></td><td>
OMM = 150 d (no P value reported)
<u>Survival rate at 1-y follow-up:</u>
DT = 52%
OMM = 28% (P = .008)
<u>Survival rate at 2-y follow-up:</u>
DT = 29%
OMM = 13% (P = .09)
<u>Percentage of patients who survived at 4-y follow-up:</u>
DT = 16.2% (11/68)
OMM = 8.2% (5/61) (no P value reported).
<u>Proportion of surviving patients who improved from NYHA Class III or IV to Class I or II at 1-y follow-up:</u>
DT = 71%
OMM = 17% (P = .0017)

Incidence of Serious Adverse Events at Final Follow-Up
<table>
<tr><th>Event</th><th>DT (Number of events)</th><th>OMM (Number of events)</th></tr>
<tr><td>Any adverse event</td><td>431</td><td>108</td></tr>
<tr><td>Bleeding</td><td>41</td><td>3</td></tr>
<tr><td>Localized infection</td><td>26</td><td>10</td></tr>
<tr><td>Sepsis</td><td>35</td><td>10</td></tr>
<tr><td>Thromboembolism</td><td>6</td><td>3</td></tr>
<tr><td>Cardiac arrest</td><td>6</td><td>6</td></tr>
<tr><td>Ventricular arrhythmia</td><td>16</td><td>22</td></tr>
<tr><td>Syncope</td><td>0</td><td>6</td></tr>
<tr><td>Nonperioperative MI</td><td>1</td><td>0</td></tr>
<tr><td>Perioperative MI</td><td>0</td><td>0</td></tr>
<tr><td>Renal failure</td><td>15</td><td>7</td></tr>
<tr><td>Hepatic failure</td><td>2</td><td>0</td></tr>
<tr><td>Other</td><td>92</td><td>41</td></tr>
<tr><td colspan="3">LVAD-specific adverse events</td></tr>
<tr><td>Right ventricular hypertrophy</td><td>11</td><td></td></tr>
<tr><td>Perioperative bleeding</td><td>28</td><td></td></tr>
<tr><td>Percutaneous site infection</td><td>24</td><td></td></tr>
<tr><td>Pump housing infection</td><td>13</td><td></td></tr>
<tr><td>Device thrombosis</td><td>3</td><td></td></tr>
<tr><td>LVAD system failure</td><td>7</td><td></td></tr>
</table>
</td><td></td></tr>
</table>

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Suspected device malfunction</td><td>58</td><td></td></tr>
</table>
<u>Cause of Death as Categorized by Authors</u>
<table>
<tr><th>Cause of Death</th><th>DT
(Number of Patients)</th><th>OMM
(Number of Patients)</th></tr>
<tr><td>Left ventricular dysfunction</td><td>1</td><td>52</td></tr>
<tr><td>Sepsis</td><td>21</td><td>1</td></tr>
<tr><td>LVAD failure</td><td>11</td><td>0</td></tr>
<tr><td>Miscellaneous noncardiovascular causes</td><td>7</td><td>0</td></tr>
<tr><td>Cerebrovascular disease</td><td>7</td><td>0</td></tr>
<tr><td>Miscellaneous cardiovascular causes</td><td>5</td><td>1</td></tr>
<tr><td>Pulmonary embolism</td><td>2</td><td>0</td></tr>
<tr><td>Acute MI</td><td>0</td><td>1</td></tr>
<tr><td>Cardiac procedure</td><td>0</td><td>1</td></tr>
<tr><td>Preoperative bleeding</td><td>1</td><td>0</td></tr>
<tr><td>Unknown</td><td>2</td><td>0</td></tr>
<tr><td>Total</td><td>57</td><td>56</td></tr>
</table>
</td><td></td></tr>
<tr><td>Lietz et al, 2007 (18)</td><td>Case series

All patients treated by PF LVAD

<u>Inclusion criteria</u>
• > 65 y
• Advanced HF ineligible for heart transplantation
• HF refractory to OMM
• NYHA Class IV for at least 60 d despite maximized oral therapy or inotropic support
• LVEF < 25%
• Peak oxygen consumption < 12 mL/kg/min</td><td>280</td><td>2001–2005</td><td>Mean 10.3 mo

All patients followed up until death, heart transplantation, or reimplantation of LVAD</td><td><u>Overall Survival (Kaplan-Meier Survival Estimates)</u>
• Median duration of LVAD support was 18.6 mo
• Survival rates were 86.1%, 56.0%, and 30.9% at 30 d, 1 y, and 2 y, respectively
<u>Survival to hospital discharge</u>
• 71% (200/280) of patients survived to hospital discharge
• 1 patient was still hospitalized at time of study closure
<u>Change in transplant eligibility</u>
Heart transplantation was reported in 17% (47/280) of patients after mean support of 10.2 mo. Change in transplant eligibility criteria was due to reversal of pulmonary hypertension (n = 12), recovery of renal function (n = 4), 5-y cancer-free survival (n = 5), weight loss (n = 3), infection (n = 4), and other (n = 16)

<u>Adverse events</u>
• Device failure, resulting in pump replacement or death, was reported in 24.6% (69/280) of patients
• Probability of device exchange or fatal device failure was 17.9% and 72.9% at 1 y and 2 y, respectively
• Death, before hospital discharge, was reported in 27.1% (76/280) of patients; 78.9% (60/76) of in-hospital deaths occurred within 3 mo

<u>Cause of Death as Categorized by Authors</u>
<table>
<tr><th>Cause of Death</th><th>Deaths,
n (%)</th></tr>
</table>
</td><td>Data were obtained from a Food and Drug Administration–mandated registry maintained by manufacturer

56 centres across country participated in data collection</td></tr>
</table>

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Sepsis</td><td>46 (29.5)</td></tr>
<tr><td>Multiorgan failure</td><td>20 (12.8)</td></tr>
<tr><td>Stroke</td><td>14 (9.0)</td></tr>
<tr><td>Right heart failure</td><td>12 (8.4)</td></tr>
<tr><td>LVAD failure</td><td>10 (6.4)</td></tr>
<tr><td>Respiratory failure</td><td>7 (4.5)</td></tr>
<tr><td>Technical</td><td>5 (3.2)</td></tr>
<tr><td>Hemorrhage</td><td>5 (3.2)</td></tr>
<tr><td>Cancer</td><td>4 (2.6)</td></tr>
<tr><td>Arrhythmia</td><td>4 (2.6)</td></tr>
<tr><td>Accident</td><td>3 (1.9)</td></tr>
<tr><td>Pulmonary embolism</td><td>2 (1.3)</td></tr>
<tr><td>Sudden death</td><td>2 (1.3)</td></tr>
<tr><td>Left ventricular failure</td><td>2 (1.3)</td></tr>
<tr><td>Other causes</td><td>12 (7.7)</td></tr>
<tr><td>Not reported</td><td>7 (4.5)</td></tr>
</table>
</td><td></td></tr>
<tr><td>Coyle et al, 2009 (19)</td><td>Case series

Patients treated by either CF or PF LVAD

Inclusion Criteria
• NYHA Class IV HF
• Contraindication to heart transplantation</td><td>58

Normal weight (BMI 30) 38

Obese (BMI ≥ 30) 20</td><td>NR</td><td>1 y</td><td>Significant Baseline Differences Between Normal and Obese Groups:
• Mean age (54.7 vs. 65.9 y)
• Incidence of diabetes (37% vs. 60%)
• Proportion of patients treated by CF LVADs (71% vs. 45%)
• Proportion of patients treated by PF LVADs (29% vs. 55%)

Outcomes at 1-Year Follow-Up
<table>
<tr><th>Outcome</th><th>Normal</th><th>Obese</th><th>P Value</th></tr>
<tr><td>Survival (% [n/N])</td><td>63 (24/38)</td><td>65 (13/20)</td><td>NS</td></tr>
<tr><td>Discharged home (% [n/N])</td><td>87 (33/38)</td><td>90 (18/20)</td><td>NS</td></tr>
<tr><td>Days on LVAD (mean ± SD)</td><td>453 ± 386</td><td>579 ± 328</td><td>NS</td></tr>
<tr><td>Mean change in weight (kg)</td><td>8</td><td>−3.5</td><td>< .05</td></tr>
<tr><td>Mean NYHA classification</td><td>1.2</td><td>1.6</td><td>NS</td></tr>
</table>
Adverse Events
LVAD pump replacement was required in 11% (4/38) of normal-weight patients and 35% (7/20) of obese patients</td><td>There were significant differences between normal and obese groups in relation to mean age (54.7 y vs. 65.9 y), incidence of diabetes (37% vs. 60%), proportion of patients treated by CF LVADs (71% vs. 45%) and proportion of patients treated by PF LVADs (29% vs. 55%)</td></tr>
<tr><td>Long et al, 2005 (20)</td><td>Case series

Patients with PF LVADs</td><td>42</td><td>2003–2004</td><td>Unclear</td><td>Survival (Kaplan-Meier survival estimates)
• Mean duration of support was 232 d
• 21% (9/42) of patients had > 300 d of LVAD support</td><td></td></tr>
</table>

<table>
<tr><th>Author, Year</th><th>Study Design and Methods</th><th>Number of Patients</th><th>Recruitment Period</th><th>Follow-up</th><th>Results</th><th>Limitations/ Comments</th></tr>
<tr><td></td><td>Inclusion Criteria
• NYHA Class IV HF
• Ineligible for heart transplantation
• Patients receiving OMM (digoxin, diuretic, beta-blocker, ACE inhibitor) for 60 of preceding 90 d
• Life expectancy < 2 y
• LVEF < 25%
• Peak oxygen consumption < 12 mL/kg/min

Patients recruited from 4 cardiac transplantation centres</td><td></td><td></td><td></td><td>• Survival rates were 90.4 ± 4.6% and 60.5 ± 9.0%, at 30-d and 1-y follow-up, respectively

Incidence of Adverse Events as Categorized by Authors
<table><tr><th>Adverse Event</th><th>Rate/Patient-Year</th></tr><tr><td>Neurologic event</td><td>0.15</td></tr><tr><td>Sepsis</td><td>0.19</td></tr><tr><td>Hepatic failure</td><td>0.04</td></tr><tr><td>Perioperative bleeding</td><td>0.15</td></tr><tr><td>Bleeding[a]</td><td>0.38</td></tr><tr><td>Localized infection</td><td>0.45</td></tr><tr><td>Percutaneous site or pocket infection</td><td>0.04</td></tr><tr><td>Right heart failure</td><td>0.08</td></tr><tr><td>Arrhythmia</td><td>0.30</td></tr><tr><td>Confirmed device failure</td><td>0.04</td></tr><tr><td>Suspected device failure</td><td>0.04</td></tr></table>[a]No further details were provided about the type of bleeding reported.

Cause of Death as Categorized by Authors
<table><tr><th>Cause of Death</th><th>Number of Patients</th></tr><tr><td>Sepsis</td><td>1</td></tr><tr><td>LVAD failure</td><td>2</td></tr><tr><td>Cardiovascular causes</td><td>1</td></tr><tr><td>Cerebrovascular disease</td><td>3</td></tr><tr><td>Multiple organ failure</td><td>3</td></tr><tr><td>Other/Unknown</td><td>3</td></tr></table></td><td></td></tr>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; BTT, bridge to transplant; CF, continuous flow; CI, confidence interval; CNS, central nervous system; DT, destination therapy; EQ-5D, European Quality of Life 5-Dimensional Utility Score; HF, heart failure; INTERMACS, Interagency Registry for Mechanically-Assisted Circulatory Support; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MLWHF, Minnesota Living With Heart Failure; NICE, National Institute for Health and Care Excellence; NR, not reported; NS, not significant; NYHA, New York Heart Association; OMM, optimal medical management; PF, pulsatile flow; RVAD, right ventricular assist device; RCT, randomized controlled trial; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure trial; SD, standard deviation; SF-36, 36-item Short Form Health Survey.

Appendix 4: Efficacy Results

Table A3: Efficacy Results Reported in Study by Jorde et al

Methods	Number of Patients	Recruitment	Follow-up	Results	Limitations
Prospective evaluation of the first PA 247 consecutive patients who underwent implantation after FDA approval of the device, Patients were preoperatively identified for DT in INTERMACS and followed for 2 years after implantation These patients were compared with HC group of the primary data cohort of 133 patients implanted with device in original trial	PA: n = 247 HC: n = 133	PA: January–September 2010 HC: March 2005–May 2007	2 y	Kaplan-Meier survival at 12 and 24 mo for PA group was 74 ± 3% and 61 ± 3% compared with HC group of 68 ± 4% and 58 ± 4% (*P* = .21). **Primary endpoint:** PA = 54% (135 of 247 patients) HC = 44% (58 of 133 patients) (*P* = .04) **Median length of hospital stay after implantation** PA 21 d HC 27 d (no *P* value reported). **Quality of life for PA Group** By 3 months the EQ-5D visual analog scale had increased approximately 30 points (from ≈40 to 70) and remained stable through 24 mo (Data reported only in graph format) **6-Minute Walk Test** At baseline: 19% of PA patients walked 180 ± 97 m 38% of HC patients walked 182 ± 140 m At 24 months: PA = 297 ± 118 m HC 372 ± 191 m (no *P* value reported)	Statistical analysis was performed by manufacturer Adverse events were reported by treating physicians and were not assessed by clinical events committee Secondary endpoints were calculated as treated. (e.g., quality of life assessments had a total of 169 patients assessed at baseline; by 24 months, 26 patients were assessed) Quality of life was assessed for PA group using the EQ 5-D. HC group was assessed with Minnesota Living with Heart Failure Questionnaire and the Kansas City Cardiomyopathy Questionnaire

Abbreviations: DT, destination therapy; EQ-5D, European Quality of Life 5-Dimensional Utility Score; FDA, Food and Drug Administration; HC, historical control; INTERMACS, Interagency Registry for Mechanically-Assisted Circulatory Support; PA, postapproval.

Appendix 5: GRADE Evidence Profile for Left Ventricular Assist Devices for Destination Therapy in Patients With End-Stage Heart Failure Who Are Ineligible for Heart Transplant

Table A4: GRADE Evidence Profile

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
	No serious limitations Serious limitations (–1)[a] Very serious limitations (–2)[a]	No serious limitations Serious limitations (–1)[a] Very serious limitations (–2)[a]	No serious limitations Serious limitations (–1)[a] Very serious limitations (–2)[a]	No serious limitations Serious limitations (–1)[a] Very serious limitations (–2)[a]	Undetected Likely (–1)[a] Very likely (–2)[a]	Large magnitude of effect (+1) Dose-response gradient (+1) All plausible confounding increases confidence in estimate (+1) Other considerations (+1)	⊕⊕⊕⊕ High ⊕⊕⊕ Moderate ⊕⊕ Low ⊕ Very Low
Survival (CF LVAD vs. OMM)							
RCTs **PF LVAD vs. OMM** RCT (REMATCH trial) and extended follow-up study (14, 16) **CF vs. PF LVADs** RCT comparing and retrospective extended follow-up study (13, 15)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (–1)[a]	Undetected	NA	⊕⊕⊕ Moderate
Observational Studies **Registry study** (INTERMACS) (12)	Serious limitations (–1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕⊕ Low
Adverse Events (CF LVAD vs. OMM)							
RCTs **PF LVAD vs. OMM** RCT (REMATCH trial) and extended follow-up study (14, 16) **CF vs. PF LVADs** RCT comparing and retrospective extended follow-up study (13, 15)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (–1)[a]	Undetected	NA	⊕⊕⊕ Moderate
Observational Studies **Registry study** (INTERMACS) (12)	Serious limitations (–1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕⊕ Low

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Quality of Life (CF LVAD vs. OMM)							
RCTs **PF LVAD vs. OMM** RCT (REMATCH trial) and extended follow-up study (14, 16) **CF vs. PF LVADs** RCT comparing and retrospective extended follow-up study) (13, 15)	Serious limitations (–1)[c]	No serious limitations	No serious limitations	Serious limitations (–1)[a]	Undetected	NA	⊕⊕ Low
Observational Studies **Registry study** (INTERMACS) (12)	Serious limitations (–1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕⊕ Low

Abbreviations: CF, continuous flow; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; INTERMACS, Interagency Registry for Mechanically-Assisted Circulatory Support; LVAD, left ventricular assist device; NA, not applicable; OMM, optimal medical management; PF, pulsatile flow; RCT, randomized controlled trial; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure.

[a]Downgraded for imprecision—optimal information size not met. Small total sample sizes in studies: REMATCH (14) N = 129; Slaughter et al (13) N = 200. In REMATCH, 2-year survival control rate = 8%. In Slaughter et al, 2-year survival control rate = 24%. REMATCH adverse event control rate unclear because data presented as only rate per patient year rather than number of patients with a specific adverse event. No raw data provided. Quality-of-life control event rate unclear. Different quality-of-life scales used within and between studies. Quality-of-life data analyzed on an as-treated basis—loss to follow-up.

[b]INTERMACS study (Kirklin et al) has limitations inherent to registry studies: not randomized; no control group; baseline characteristics/similarities of patients not reported; patients enter registry over different periods; not blinded. (12) Baseline characteristics of patients not reported (possible unknown confounding factors). Of 1,287 patients, only 31 were treated by biventricular assist devices and were included in analyses.

[c]Quality-of-life analyses were secondary analyses and were analyzed on an as-treated basis. Because it was impossible to ensure patients and investigators were blinded, there was potential for bias regarding patient-reported outcomes. Various quality-of-life scales were used in studies.

Appendix 6: Status Internationally

In the United Kingdom, the National Institute for Health and Care Excellence (NICE) published a draft consultation document that makes the following provisional recommendations (40):

> *Current evidence on the efficacy and safety of the implantation of a left ventricular assist device for destination therapy in people ineligible for heart transplantation is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit. For people who are eligible for heart transplantation, refer to NICE's interventional procedure guidance on short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery.*
>
> *Patient selection should be done by a multidisciplinary team that includes a cardiologist with a specialist interest in heart failure, a cardiothoracic surgeon and a cardiac anaesthetist.*
>
> *Implantation of left ventricular assist devices for destination therapy should be done by surgeons, anaesthetists and intensive care specialists with special training and regular practice in performing this procedure and caring for these patients. Subsequent care should be provided by a multidisciplinary team including staff with the expertise to deal with patients' medical and psychological management, and with the maintenance of their left ventricular assist devices.*
>
> *Clinicians should enter details on all patients who have a left ventricular assist device for destination therapy onto the UK Central Cardiac Audit Database.*

In the United States, the Centers for Medicare and Medicaid Services (CMS) determined (41):

> *The evidence is adequate to conclude that VAD implantation as destination therapy improves health outcomes and is reasonable and necessary when the device has received FDA approval for a destination therapy indication and only for patients with New York Heart Association (NYHA) Class IV end-stage ventricular heart failure who are not candidates for heart transplant and who meet all of the following conditions:*
>
> a. *Have failed to respond to optimal medical management (including beta-blockers, and ACE inhibitors if tolerated) for at least 45 of the last 60 days, or have been balloon pump dependent for 7 days, or IV inotrope dependent for 14 days; and,*
> b. *Have a left ventricular ejection fraction (LVEF) < 25%; and,*
> c. *Have demonstrated functional limitation with a peak oxygen consumption of ≤ 14 ml/kg/min unless balloon pump or inotrope dependent or physically unable to perform the test.*

Appendix 7: Summary of Studies

Table A5: Summary of Studies for Continuous-Flow LVAD

Author, Year	General Information	Cost Information (Perspective, Currency, Year, Costs)	Survival	Quality of Life	Results for LVAD as Destination Therapy
Long et al, 2014 (26)	*Design* Decision-analytic model to estimate survival and costs among patients with OMM–dependent stage D heart failure under different treatment strategies *Population* Transplant-ineligible patients, OMM vs. DT LVAD *Time horizon* Lifetime *Discount rate* Costs and QALYs, 3%	*Perspective* Society *Currency, year* 2012 US dollars *Costs (lifetime)* OMM: $112,600 USD DT LVAD: $593,000 USD	Contemporary survival rates for LVAD patients were derived from INTERMACS Average life expectancy with OMM was 9.4 months with a 1-year survival of 26%, vs. 4.42 years in heart transplant–ineligible patients (DT LVAD), generating 1-year and 2-year survival rates of 78% and 62%, respectively, or 4.42 LYG 5-year survival was 32%	QALYs: 2.79 for LVAD vs 0.78 for OMM (Net of 2.38 QALYs)	From extrapolation of recent constant hazard rates beyond the first year, LVAD patients were estimated to live 4.42 years on average This strategy cost $201,600/QALY gained, relative to OMM; patient's age, time on wait list, and costs associated with care influenced outcomes $131,800 per LYG
Neyt et al, 2013 (27)	*Design* CUA, Markov model *Population* Adults with chronic end-stage heart failure, contraindications for a heart transplant, LVEF of ≤ 25%, and NYHA class IV for at least 90 days despite OMM; CF LVAD as DT vs. OMM *Time horizon* Lifetime *Discount rate* Costs 4%, effects, 1.5%	*Perspective* Society *Currency, year* 2010 Euros *Costs*[a] LVAD implantation: €126,505 (including LVAD device cost of €70,000) Rehospitalization (excluding LVAD replacement): €8,118 Number of repeat hospitalizations: HM-II, 2.64 per patient-year; OMM, 3.15 per patient-year Discounted incremental cost: €299,100 (95% CI, €190,500–€521,000)	*Extrapolation past 24 months (base-case scenario)* • OMM[b]: 2-year survival of 13%; no survival after 3 years • CF LVAD[c]: the monthly mortality during the second year was used to extrapolate results. Age- and gender-adjusted increase in monthly mortality risk was applied according to Dutch life tables Discounted incremental effect 3.23 LYG (95% CI, 2.18–4.49)	LVAD: 0.809 (95% CI, 0.745–0.873) OMM: 0.548 (95% CI, 0.389–0.708) Discounted incremental effect: 2.83 QALYs gained (95% CI, 1.91–3.90)	ICER: €107,600/QALY (95% CI, €66,700–€181,100) (2.83 QALYs gained and additional cost of €299,100) and €94,100/LYG (95% CI, €59,100–€160,100) (3.23 LYG and additional cost of €299,100)

Rogers et al, 2012 (28)	*Design* CEA, Markov model *Population* Patients with predominantly NYHA class IV symptoms and an LVEF of ≤ 25%; patients were ineligible for heart transplantation; CF LVAD for DT vs. OMM *Time horizon* 5 years *Discount rate* 3% for costs and effects	*Perspective* Third-party payer *Currency, year* 2009 US dollars *Costs* LVAD implantation hospital cost: $193,812 USD LVAD implantation professional service cost: $8,841 USD LVAD replacement cost: $131,430 USD Monthly LVAD replacement rate: 0.005 Rehospitalization cost (per event): $6,850 USD Monthly rehospitalization rate for LVAD: 0.21 Monthly rehospitalization rate for OMM: 0.1325 Monthly outpatient costs (LVAD and OMM): $2,331 USD End-of-life cost (LVAD and OMM): $44,211 USD Total costs (discounted): CF LVAD $360,407 USD; OMM $62,856 USD Incremental cost: $297,551 USD	DT trial Extrapolation past 24 months was based on an exponential survival curve using the constant hazard rate observed over 24 months • OMM[d]: 0.105 per month • CF LVAD[e]: 0.023 per month (base-case analysis) LVAD vs. OMM: 2.42 vs. 0.64 LYG	Mean utility values of 0.855, 0.771, 0.673, and 0.532 for NYHA classes I, II, III, and IV, respectively Probability of belonging to a specific NYHA class: monthly estimates obtained from the REMATCH (30) and HeartMate II DT trials for the OMM and LVAD arms (probabilities of being in NYHA I–IV at 0, 1, 3, 6, 9, 12, 18 and 24 months in original text) LVAD vs. OMM: 1.87 vs. 0.37 QALYs	ICER: $198,184 USD/QALY (1.5 QALYs gained and additional cost of $297,551 USD) and $167,208 USD/LYG (1.78 LYG and additional cost of $297,551 USD)

Abbreviations: CF, continuous-flow; CI, confidence interval; CUA, cost-utility analysis; HM-II, Heartmate II; ICER, incremental cost-effectiveness ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; KM, Kaplan-Meier; LVAD, left ventricular assistive device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OMM, optimal medical management; QALY, quality-adjusted life-year; LYG, life-year gained ; QOL, quality of life; REMATCH, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure; UMC, University Medical Center Utrecht

[a]Data from UMC Utrecht (69 patients with HM-II implantation as bridge to transplantation).

[b]Survival from the REMATCH trial.

[c]Survival from the HeartMate II Destination Therapy trial.

[d]Kaplan-Meier survival curve from the REMATCH trial.

[e] Kaplan-Meier survival curve from the HeartMate II Destination Therapy trial.

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