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Use of Left Ventricular Assist Devices as Destination Therapy in End-Stage Congestive Heart Failure: A Systematic Review

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PREFACE

Quality Enhancement Research Initiative's (QUERI) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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INTRODUCTION

Several common chronic conditions such as atherosclerotic heart disease and hypertension as well as other diseases can result in heart failure, a reduced ability of the heart to pump blood and maintain normal bodily functions. The prevalence of chronic heart failure increases with age to over 10% in the elderly population.[7] More than 100,000 people in the United States with progressive heart failure are refractory to available treatments and have high rates of hospitalization and mortality and a poor quality of life due to limited physical and social activities and psychological stress. Heart transplantation is currently the preferred treatment for end-stage heart failure. Unfortunately, the supply of donor hearts is far less than needed and many patients do not meet the criteria for heart transplantation primarily due to old age and comorbidities such as diabetes with damage to vital organs, pulmonary hypertension, renal insufficiency, malignancies and morbid obesity.

Implantable mechanical pumps that assist the circulation of blood by one or both ventricles of the heart have evolved over several decades. Typically blood flows from the native left ventricle of the heart into the surgically implanted assist device and is pumped out into the aorta via an implanted conduit. The design of the mechanical pump varies (pulsatile fill and pump designs similar to a normal heart and continuous flow rotary pumps). Currently, long-term implantable left ventricular assist devices require an external source of power and control module.

Surgical placement of a left ventricular assist device is increasingly done as a last resort for patients with refractory heart failure who are not eligible for heart transplantation, so called destination therapy.[8] Some patients may improve after they receive a ventricular assist device as destination therapy and become eligible for heart transplantation even though this was not the initial therapeutic goal. A limited number may recover enough heart function to not need a heart transplant or mechanical assist device. Although survival with a newer generation continuous flow ventricular assist device is approaching that of a heart transplant, long-term use of the device by patients who are eligible for a heart transplant is not currently accepted practice.[9] Conversely, many patients that receive a ventricular assist device as a bridge to transplant use the device for increasingly prolonged periods while waiting for a donated heart and some may become ineligible for a heart transplant.

The purpose of this report is to review the scientific evidence for use of ventricular assist devices as destination therapy for patients with severe, refractory heart failure who are not eligible for heart transplantation at the time the device is implanted. Although many patients receive the same types of ventricular assist devices as a bridge to heart transplantation or recovery, the characteristics, hence risk profiles, of patients receiving bridge therapy are different from patients selected to receive a device as permanent destination therapy. Furthermore many bridged patients do receive a heart transplant that alters patient outcomes. Thus, this review focused on evidence about patient outcomes, patient selection and cost

effectiveness of ventricular assist devices specifically intended as destination therapy. The primary goals of destination therapy are to:

- prolong survival,
- improve daily function and health-related quality of life,
- minimize harms including infection, major bleeding episodes, thromboembolic events including strokes and device malfunction or failure especially those that require hospital care.

VENTRICULAR ASSIST DEVICES APPROVED FOR USE AS DESTINATION THERAPY

The first randomized controlled clinical trial of a ventricular assist device as destination therapy compared an early generation device (a ventilated electric pulsatile pump, HeartMate VE) to optimal medical therapy.[2] This device significantly improved survival to 52% versus 25% at 1 year and 23% versus 8% after 2 years. Unfortunately, 35% of the surgically implanted devices failed within 2 years, and 17% of the deaths were attributed to failure of the device. The overall effect of the device, including serious complications on the subjects' functional status and health-related quality of life, was difficult to assess due to the high, differential mortality rates and lack of assessments during early follow-up. Comparisons of the subjects that survived for one year indicated physical and emotional status were better in the group treated with the ventricular assist device. This pivotal trial led to approval by the U.S. Food and Drug Administration (FDA) in November 2002 of the left ventricular assist device (modified and now known as the HeartMate XVE) for use as destination therapy.[10] The approved indication included patients that were not eligible for heart transplantation who have New York Heart Association (NYHA) class IV heart failure (shortness of breath and/or fatigue during minimal physical activity or at rest) for at least 60 of the last 90 days despite optimal medical therapy, an unassisted left ventricular ejection fraction less than 25%, and a peak oxygen consumption less than 12 ml/kg/min during an exercise stress test or continued need for an intravenous inotrope. Furthermore, the estimated life expectancy without the ventricular assist device should be less than 2 years, similar to patients that participated in the clinical trial. After FDA approval, clinical use of the HeartMate XVE was associated with a similar 56% 1-year survival, but unfavorable rates of surgical complications including sepsis, multi-organ failure, right heart failure, prolonged hospitalization and a 90-day in-hospital mortality of 27%.[11] Within 2 years, 73% needed device replacement or experienced a fatal device failure.

In January 2010, a newer generation, rotary continuous flow ventricular assist device (HeartMate II) was approved by the FDA for destination therapy based on a clinical trial that compared the new ventricular assist device, the HeartMate II, to the HeartMate XVE.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS) COVERAGE

In October 2003, the Centers for Medicare and Medicaid Services (CMS) decided to cover use of FDA-approved ventricular assist devices as destination therapy when provided by a Medicare-

approved heart transplantation center.[12] The clinical center needed to have the staff and processes to fully inform prospective recipients about the potential benefits, risks and required follow-up care. Furthermore, the center was required to report case information to a national audited registry from the date of device implantation until death. In March 2007, the facility criteria were modified to require a board-certified cardiovascular surgeon that has implanted at least 10 ventricular assist devices during the past 3 years (at least one in past 18 months) and facility certification by the Disease-Specific Care Certification Program for Ventricular Assist Device developed by the Joint Commission on Accreditation of Healthcare Organizations.

After FDA approval of the HeartMate II device for destination therapy, CMS eligibility requirements were changed to include patients that are refractory to optimal medical management for at least 45 of the past 60 days or dependent on an intra-aortic balloon pump for 7 days or an intravenous inotrope for 14 days. The peak oxygen requirement was increased to 14 ml/kg/min or less unless the patient was physically unable to do an exercise test or was dependent on a balloon pump or intravenous inotrope.

REGISTRY OF VENTRICULAR ASSIST DEVICES USED AS DESTINATION THERAPY

An Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) was created with support from the National Heart, Lung and Blood Institute, FDA, CMS, the device industry and health care providers. In June 2006, this registry began to collect information about patients, devices and outcomes including adverse events. The registry is focused on use of FDA-approved ventricular assist devices including destination therapy. The registry meets the CMS mandate that all hospitals in the United States that provide mechanical circulatory support as destination therapy enter their cases into a national audited registry.[3] During the 6-month period from January to June 2010 (shortly after FDA approval of the new continuous flow device, HeartMate II), there was nearly a 10-fold increase in the number of registered uses for destination therapy. All registered cases during this period received the newer FDA-approved HeartMate II ventricular assist device. As of June 30, 2011, 126 medical centers had registered patients of which 101 centers were approved by CMS to provide destination therapy.[13] A total of 847 patients treated with destination therapy had been registered and all recent cases employed the FDA approved continuous flow ventricular assist device, presumably HeartMate II. *No VA Medical Centers were listed by the registry as of March 5, 2012 (see www.intermacs.org/membership).* Patients receiving a continuous device as destination therapy had significantly worse survival than those receiving a continuous device as a bridge to transplant.

GUIDELINE RECOMMENDATIONS

A 2009 update of the 2005 American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines for the Diagnosis and Management of Heart Failure in Adults did not modify their previous recommendation concerning destination therapy for patients with refractory end-stage heart failure (stage D).[14] Consideration of a permanent left ventricular assist device continued to be considered reasonable for highly selected (undefined) patients that have estimated 1-year mortality with optimal medical therapy over 50%. This

recommendation was developed in collaboration with International Society for Heart Lung Transplantation.

Guidelines issued by the Heart Failure Society of America in 2010 recommend that permanent mechanical assistance may be considered in highly selected patients with severe heart failure refractory to conventional therapy who are not candidates for heart transplantation, particularly those who cannot be weaned from inotropic support by an experienced heart failure center.[15]

The 2011 Canadian Cardiovascular Society Heart Failure Guidelines recommend that permanent mechanical circulatory support be considered for highly selected patients who are ineligible for heart transplantation.[16] This was considered to be a 'weak' recommendation because of the uncertainty about the balance of benefits and risk given currently available evidence. Eligible candidates would have severe symptoms of advanced heart failure despite optimal treatment and meet at least two of the following criteria: 1) a left ventricle ejection fraction less than 25% and, if exercise stress test is done, a peak oxygen consumption less than 14 ml/kg/min, 2) progressive organ dysfunction due to hypoperfusion, 3) need to reduce standard therapies for heart failure due to symptomatic hypotension or worsening renal function, 4) more than 3 hospital admissions for refractory heart failure during the previous year or 5) unable to wean from inotropic support. Informed patient preferences were a very important component of the recommendation as was a medical center that has a multidisciplinary team with expertise in surgical implantation and follow-up of patients with ventricular assist devices.

METHODS

TOPIC DEVELOPMENT

This project was nominated by Dr. Chester Good, Chief, Section of General Medicine. The key questions were developed with input from a technical expert panel (see Appendix A).

The final key questions were:

Key Question #1. How does use of an FDA-approved, current generation LVAD as destination therapy (i.e., the HeartMate II left ventricular assist device) effect patient outcomes?

Key Question #2. What patient or site characteristics have been associated with patient benefits or harms when the FDA-approved, current generation LVAD is used as destination therapy?

Key Question #3. What is the range of cost-effectiveness estimates of using the FDA-approved, current generation LVAD as destination therapy in end-stage heart failure and what explains variation in these estimates?

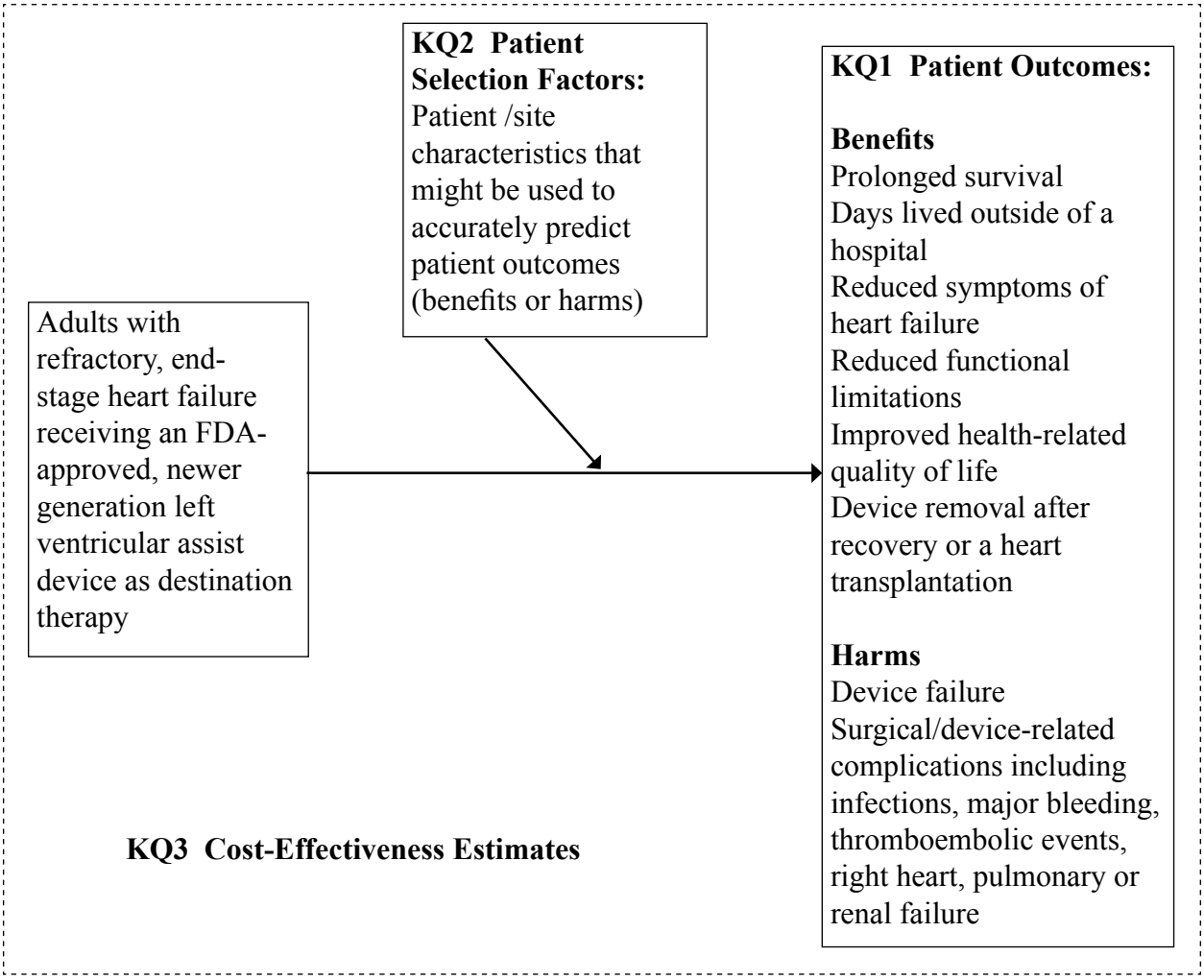
Figure 1 depicts the analytic framework for these questions.

SEARCH STRATEGY

We searched MEDLINE (OVID) for studies that reported patient outcomes, articles about patient selection or prediction of patient outcomes, systematic reviews or cost-effectiveness analyses from 1995 to October 2011 using standard search terms. The 1995 start date is well before the first randomized clinical trial that used a left ventricular assist device for destination therapy. The search was limited to articles involving human subjects and published in the English language. Search terms included: heart-assist devices, heart failure and ventricular dysfunction (See Appendix B for the MEDLINE search strategy). We also examined reference lists to identify other pertinent publications and asked our panel of experts to identify additional reports.

Other searches included the Cochrane Database of Systematic Reviews, the Translating Research into Practice (TRIP) database for systematic reviews and technology assessments, the Center for Medicare and Medicaid Services (CMS) Web site and the NIH Clinical Trials Web site.

Figure 1. Analytic Framework



STUDY SELECTION

Generally, abstracts and full text articles were excluded whenever

1. The report did not provide data about the only continuous flow device currently approved by FDA for destination therapy, the HeartMate II ventricular assist device.
2. The report did not provide data about use of the device as destination therapy. Short-term use of the device as a bridge to transplant was excluded.
3. The report did not provide data about patient outcomes of interest such as survival, hospitalizations, daily function, health-related quality of life or harms.
4. The report did not provide data about adults defined as age 18 years or older.

The following discusses more specific study selection criteria for each key question.

Key Question #1 – Patient Outcomes

Randomized controlled trials were sought as the highest quality of evidence for the first key question about patient outcomes. At a minimum, randomization helps assure unbiased allocation of subjects to the groups being compared. However, the number of patients currently eligible for destination device therapy is limited and randomization might not balance baseline characteristics in small studies. Subjects that withdraw from the study after randomization or crossover to the comparison group may also bias the comparison, particularly if any changes in treatment were related to study outcomes. Obviously a comparison of a surgically implanted device to continuation of optimal medical therapy can't be blinded, and endpoint assessments, especially subjective assessments and device-related harms, may be biased as a result. However, more objective endpoints such as maximal exercise tests are affected by patient effort and difficult to interpret in terms of how they translate into affects on patients' lives. Given the high morbidity and mortality of patients with refractory end-stage heart failure, randomization to continuation of non-surgical therapies might not be acceptable to patients and providers who believe a ventricular assist device is a reasonable alternative. Therefore, randomized clinical trials are being designed as a non-inferiority comparison of a new ventricular assist device to an approved device.[17,18] Non-inferiority studies introduce additional concerns that the characteristics of the enrolled subjects, including how they were treated, might not be similar to previous studies that demonstrated the 'control' device is effective with acceptable risks.[19] Furthermore, the magnitude of the differences between devices excluded by the statistical analysis of non-inferiority needs to be small enough to rule out clinically important differences. Since high quality evidence from randomized clinical trials of the FDA-approved continuous flow ventricular assist device for destination therapy is very limited, we did not restrict our review to randomized controlled trials, and considered cohort studies that could provide estimates of the likelihood of patient outcomes.

Key Question #2 – Patient Selection

Given numerous differences in outcomes including device malfunction between the two ventricular assist devices currently approved for use as destination therapy, the HeartMate XVE and HeartMate II, and the current exclusive use of the HeartMate II device for destination therapy in the INTERMACS registry, our search for the second key question concerning selection of patients sought specific analyses about the HeartMate II ventricular assist device. As previously mentioned, we also focused on selection of patients for destination therapy rather than bridge therapy because the criteria and outcomes including competing risks such as heart transplantation are not the same. Thus, studies were selected if they provided evidence specifically or predominantly about the selection of patients for use of the HeartMate II device as destination therapy. Subgroup analyses that focused on this specific therapy were considered including regression analysis that included variables indicating the type of ventricular assist device and/or therapy.

Patient selection criteria for destination therapy are based primarily on the selection criteria used in the studies that supported FDA approval and therefore define patients eligible for the approved indication. However, regression or subgroup analyses are often conducted using study data or other patient cohorts in an effort to better define which patients are more likely to benefit or be harmed. Studies were sought that provided statistical evidence for significant differences in

patient outcomes between groups defined by preoperative patient characteristics. Expert reviews of patient selection criteria were read in search of additional scientific evidence about patient selection criteria. Because estimates of patient survival without the ventricular assist device are used to select patients, we also included studies that evaluated survival prediction models in a sample of patients eligible for destination therapy.

Key Question #3 – Cost Effectiveness

We included studies that provided cost-effectiveness estimates for the use of HeartMate II ventricular assist device as destination therapy.

DATA ABSTRACTION

For reports that provided pertinent evidence about patient outcomes and selection (Key Questions #1 and #2), we extracted information about the study sites and sponsor, subject inclusion and exclusion criteria, sample characteristics, intervention(s) including the comparison group(s), if any, length of follow-up, patient outcome(s) of interest and quality of the evidence.

For reports that provided pertinent evidence about cost effectiveness (Key Question #3), we extracted information about the overall estimate of cost effectiveness, the uncertainty in the cost effectiveness estimate, the base case assumptions for the cost effectiveness model and the results of sensitivity analyses that varied the assumptions in the base case model.

QUALITY ASSESSMENT

Key Question #1 – Patient Outcomes

The quality of clinical trials was judged based on the potential for bias in the estimates of treatment effects according to the following criteria: 1) random assignment to treatment with adequate concealment of assignment, 2) blinding of key study personnel (i.e., providers, study personnel and/or patients) who determined outcomes to assigned treatment, 3) analysis by intention-to-treat (i.e., all subjects counted in group to which they were randomized in the analysis of outcomes), 4) reporting of number of withdrawals/dropouts by group assignment along with reasons for any losses to follow-up that may be related to beneficial or adverse treatment effects and 5) the size of the treatment effects (larger effects are less likely to be explained by baseline differences between treatment groups or differential losses to follow-up).[20] Studies were rated as good, fair, or poor quality. A rating of 'good quality' generally required that the investigators randomly assigned patients to treatments and reported adequate concealment of assignments, blinded or objective outcome assessments, an intent-to-treat analysis, an adequate description of reasons for dropouts/attrition and a sizable treatment effect. The quality of a study was generally considered poor if the method of allocation concealment was inadequate or not defined, blinding was not reported or possible, analysis by intent-to-treat was not reported and reasons for dropouts/attrition were not reported and/or there was a high rate of attrition or the estimated treatment effect was small.

Key Question #2 – Patient Selection

Criteria to assess the quality of evidence concerning variables and multivariable models to predict patient outcomes have not been firmly established. We relied on our, as yet unpublished, guidance for conducting systematic reviews of prognostic tests commissioned by the Agency for Healthcare Research and Quality (Rector TS, Taylor BG, Wilt TJ. Chapter 12: Systematic Reviews of Prognostic Tests in *Methods Guide for Comparative Effectiveness Reviews*). Specific criteria: 1) were patients in the analysis similar to those who would receive an FDA-approved ventricular assist device as destination therapy?, 2) were the variables used to make outcome predictions measured shortly before implantation of the device and not affected by the procedure, subsequent care or knowledge of the outcome being predicted?, 3) were the measurements of the potential predictor variables and outcomes reliable, valid and routinely available in clinical practice?, 4) did losses to follow-up bias the assessment of outcomes?, 5) was the duration of follow-up adequate?, 6) were the number of patients that had the outcome being predicted adequate for the number of predictors tested?, 7) were predicted outcome probabilities reported for patient subgroups that would be included or excluded from destination therapy?, 8) how closely did outcome predictions agree with the observed outcomes?, 9) were the outcome prediction somehow validated? and 10) did the analysis demonstrate that the outcome predictions could be used to improve patient outcomes?

Key Question #3 – Cost Effectiveness

There are no well-accepted criteria for evaluating the quality of cost-effectiveness analyses, however, there are long lists of factors related to the analytical model and assumptions that can be considered.[21] In order to assess quality we extracted information on the cost-effectiveness model structure and assumptions.

RATING THE BODY OF EVIDENCE

The overall evidence for a key question was graded using the method proposed by Owens et al.[23] using the following criteria:

- High grade evidence: Further research is very unlikely to change the confidence in the estimated treatment effect on patient outcomes. Generally, a high grade requires more than one good quality study and consistent estimates with statistical confidence intervals that exclude clinically meaningful differences.
- Moderate grade evidence: Further research may change the estimate of the size of the effect or the level of uncertainty.
- Low grade evidence: Further research is likely to change the estimate of the size of the effect and or the confidence interval.
- Insufficient evidence: Sufficient evidence was not found to answer the question.

DATA SYNTHESIS

We constructed evidence tables for Key Questions #1, #2 and #3, and drew our conclusions based on a qualitative synthesis of the evidence available to answer each key question. Not finding several reports that provided independent estimates of patient outcomes, relationships between baseline variables and patient outcomes or cost effectiveness, we did not do any meta-analyses to pool evidence from different studies.

PEER REVIEW

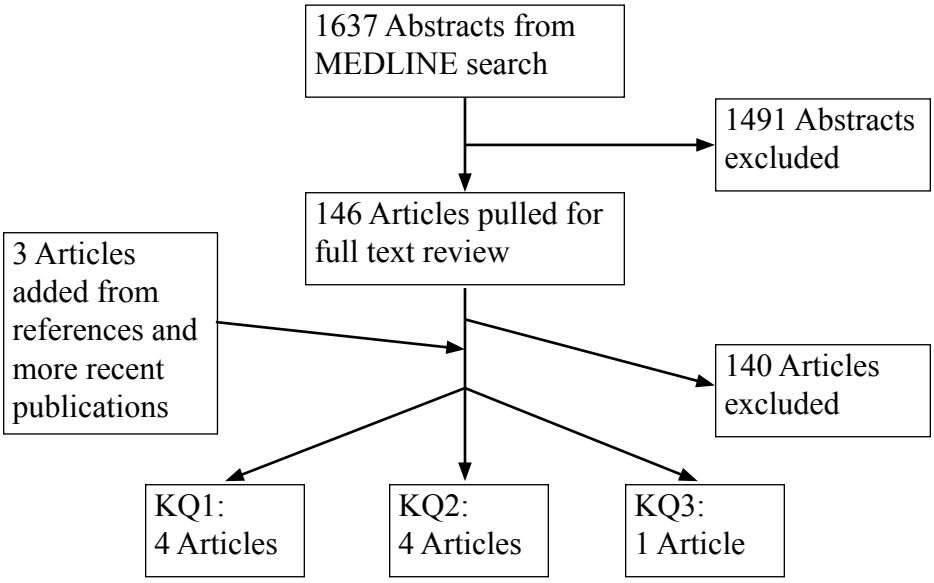
A draft version of this report was reviewed by clinical experts including the Technical Expert Panel. Their comments are presented in Appendix C as are our responses to any suggestions to modify the report itself.

RESULTS

LITERATURE SEARCH

Figure 2 summarizes the literature search. We reviewed 1,637 titles and abstracts from the electronic search. After applying inclusion/exclusion criteria, 1,491 references were excluded. We retrieved 146 full-text articles for further review and 140 were excluded. We identified 1 additional reference by hand-searching references lists and 2 articles that were published after our search date. There were a total of 4 articles (3 from the literature search) for Key Question #1; only one was a randomized controlled trial. There were 4 articles included for Key Question #2 (3 from the literature search); 3 examined prediction models and 1 was a subgroup analysis. For Key Question #3, 1 article was included that was published after the initial literature search.

Figure 2. Literature Flow Diagram



KEY QUESTION #1. How does use of an FDA-approved, current generation LVAD as destination therapy (i.e., the HeartMate II left ventricular assist device) effect patient outcomes?

We found one good quality randomized clinical trial of the HeartMate II left ventricular assist device employed as destination therapy.[1] Patients enrolled in this study generally met the current criteria for destination therapy that were based on a previous study of an older generation device[2] including being ineligible for a heart transplant, most being in NYHA association class IV heart failure that was refractory to optimized therapies, a left ventricular ejection fraction less than 25% and very limited ability to exercise. The subjects' (n=200) mean age was 62 years and 84% were males. Compared to the older generation HeartMate XVE left ventricular assist device, use of the HeartMate II provided superior patient outcomes (See Appendix D, Table 1). After 24 months, the primary endpoint of survival free of disabling stroke or reoperation to remove the device was 46% versus 11%, respectively ($p < 0.0001$). Survival in the HeartMate II group was

significantly better (58% versus 24% after 2 years) and subjects spent a greater percentage of their follow-up time outside of a hospital (88% versus 74%) largely due to a lower readmission rate. During follow-up, survivors with the HeartMate II also had fewer limitations due to heart failure as measured by the NYHA class, Minnesota Living with Heart Failure Questionnaire and clinical component of the Kansas City Cardiomyopathy Questionnaire. The incidences of several adverse events were lower as well including right heart failure, cardiac arrhythmias, device-related infections, sepsis, respiratory failure, renal failure and device replacement. None of the adverse events rates were higher in the HeartMate II group including major bleeding and strokes. This study provides moderate quality evidence that numerous patient outcomes in patients treated with the HeartMate II are better than the HeartMate XVE when used for destination therapy. Since patient characteristics and outcomes in the HeartMate XVE arm of this study were similar to those in the previous clinical trial that demonstrated the HeartMate XVE provided superior outcomes compared to optimal medical therapy,[2] one might infer that the HeartMate II would also be superior to optimal medical therapy.

A recent fair quality report[23] compared outcomes of patients enrolled in a continued access protocol to those who received the HeartMate II in the above randomized clinical trial (Appendix D, Table 1). Patient selection criteria and baseline characteristics in the continued access protocol were essentially the same as the randomized controlled trial. The patients enrolled in the continued access protocol had as good or better outcomes. After 24 months, the primary endpoint of survival free of disabling stroke or reoperation to remove the device was 50% in the group assigned to the HeartMate II in the randomized controlled trial versus 59% in the continued access protocol (p=0.07). Survival for 2 years was also similar 58% versus 63%, respectively. During follow-up survivors also had similar improvements in symptoms and related quality of life as measured by the NYHA class, Minnesota Living with Heart Failure Questionnaire and the Kansas City Cardiomyopathy Questionnaire. The incidences of hemorrhagic stroke, bleeding treated with packed red blood cells, sepsis and device-related infection were significantly lower in the group enrolled in the continued access protocol. The reduction in bleeding events was attributed to changes in the postoperative use of less aggressive anticoagulation regimens. There were no differences in the incidences of other adverse effects.

Two reports of case series[3,24] provided survival estimates for patients receiving the Heart Mate II as destination therapy (Appendix D, Table 1). Although these reports provided lower quality evidence, survival at one year in these cases series was similar to the 68% 1-year survival in the HeartMate II group in the randomized clinical trial. More recent survival estimates without heart transplantation or heart recovery from the INTERMACS registry that are based on 740 cases were 74% and approximately 60% after 1 and 2 years, respectively.[13] The available survival estimates are remarkably consistent with each other.

Summary of Findings for Key Question #1

A single good quality study provided evidence that use of the newer, continuous flow HeartMate II ventricular assist device for destination therapy provides better patient outcomes than the older, pulsatile flow HeartMate XVE device. A fair quality continued access protocol for use of the HeartMate II indicated that all of the reported patient outcomes continue to be as good as those seen in the randomized controlled trial or better including significantly fewer hemorrhagic

strokes, major bleeding episodes and infections. Case series have also reported similar survival when the HeartMate II was used as destination therapy.

Clinical trials of other continuous flow devices for destination therapy such as a HeartWare device with a different continuous flow design are ongoing,[4,5,25] however results are not expected for several years.

KEY QUESTION #2. What patient or site characteristics have been associated with patient benefits or harms when the FDA-approved, current generation LVAD is used as destination therapy?

Based on the approved FDA indication and clinical trials, CMS has determined that the evidence is adequate to conclude that implantation of a left ventricular assist device approved by the FDA for destination therapy is reasonable and necessary for Medicare beneficiaries who have chronic end-stage heart failure, are not candidates for heart transplantation, and meet all of the following conditions: 1) NYHA Class IV symptoms of heart failure that have not responded to optimal medical management including dietary salt restriction, diuretics, digitalis, beta-blockers and angiotensin converting enzyme inhibitors (if not tolerated, presumably angiotensin receptor blockers would be an acceptable alternative) 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 (cardiac resynchronization therapy and an implantable cardiac defibrillator are not listed although they have become standards of care when clinically indicated for patients with heart failure), 2) a left ventricular ejection fraction less than 25%, 3) demonstrated functional limitation with a peak oxygen consumption of 14 ml/kg/min or less unless the patients is balloon pump or inotrope dependent or physically unable to perform an exercise test and 4) appropriate body size for the device.[12]

In addition, CMS determined that destination therapy is reasonable and necessary only when the procedure is performed in a facility approved under the Disease-Specific Care Certification Program for Ventricular Assist Device developed by the Joint Commission on Accreditation of Healthcare Organizations.[26] Facility staff must have implanted at least 10 ventricular assist devices or total artificial hearts as a bridge to transplant or as destination therapy during the past 36 months with at least one procedure within the past 18 months. The facility also must have in place staff and processes that assure that prospective recipients receive all information necessary to assist them in giving informed consent for the procedure, and so that they and their families are fully aware of the aftercare requirements and potential limitations as well as benefits. We found only one study of patient preferences related to use of ventricular assist devices that explored a few hypothetical situations describing life expectancy and daily function without the device.[27]

The CMS criteria also state that the facility must be an active, continuous member of a national, audited registry that requires submission of data on all destination therapy patients from the date of implantation throughout the remainder of the recipient's lives. The INTERMACS registry satisfies this CMS reporting requirement.

More detailed patient inclusion and exclusion criteria have been used in clinical trials of ventricular assist devices as destination therapy and are recommended by clinical experts.[28,29,30,31,32]

Since outcomes among patients meeting current selection criteria do vary, selection of patients could be refined using strong predictors of patient outcomes. Clearly, there is little or no benefit to patients that don't recover from the operation to implant a ventricular assist device. A validated method to determine which eligible patients have unacceptably high (not defined) operative risk might improve patient selection and outcomes. A report of INTERMACS data summarized in Appendix D, Table 2 indicated that the presence of cardiogenic shock, concomitant surgery and poorer renal function as indicated by higher blood urea nitrogen were associated with higher mortality within 30 days of the operation.[3] This analysis focused on use of ventricular devices as destination therapy but included many cases that received the obsolete HeartMate XVE. Interactions between the type of device and operative risk factors were not reported to determine whether the prognostic information depended on the type of device. More importantly, the risk factors were not used to identify patients that have an unacceptably high operative risk, and the confidence one would have in selecting patients based on the predicted probabilities of operative mortality risk was not reported.

Lietz et al. analyzed data in the manufacturer's registry of HeartMate XVE use post-FDA approval to develop a risk model of 90-day in hospital mortality.[11] The risk model incorporated several preoperative variables as summarized in Appendix D, Table 2. The risk score derived from this model discriminated the two outcome groups and could place patients into risk groups that had substantially different levels of risk. However, the difference in predicted and observed outcomes was substantial in some risk groups and the precision of the estimates was inadequate in the smaller risk groups. Furthermore, there was no consensus about which, if any, risk groups should be excluded from treatment due to high risk. We found no reports that tried to validate or update this risk model for current practices that use the HeartMate II device.

Current criteria for use of a ventricular assist device as destination therapy include an estimated 1-year survival without the device of less than 50%[14] or an overall life expectancy of less than 2 years.[10,12] A validated method for making these predictions has not been established. As summarized in Appendix D, Table 2, Levy et al. adapted and evaluated the Seattle Heart Failure Model to predict survival of the patients in the optimal medical therapy arm of the initial clinical trial of the HeartMate VE.[33] There was good agreement between the observed and predicted 1-year survival (28% versus 30%), and 81% met the guideline criterion of less than 50% predicted probability of survival for one year without a ventricular assist device. No further studies were found that indicated use of this prediction model would improve selection of patients for destination therapy or patient outcomes.

A secondary analysis of clinical trial data collected at a single center suggested that carefully selected patients that were 70 years old or older (a commonly used cutoff for heart transplantation) had similar outcomes to those less than 70 years old.[34] However as summarized in Appendix D, Table 2, there were only a small number of patients in this comparison and there were no adjustments for preoperative differences.

Summary of Findings for Key Question #2

The scientific evidence concerning use of newer generation, continuous flow FDA-approved ventricular assist devices, i.e., the HeartMate II, is insufficient to refine patient selection criteria for destination therapy beyond the current criteria used to enroll patients in the pivotal clinical trials and determine eligibility for CMS coverage.

A few studies have identified risk factors for mortality and developed or applied prediction models to this particular patient population. Further studies are needed to validate the use of different criteria to select patients and improve patient outcomes. An ongoing clinical trial is selecting less severely ill patients and may expand the criteria for use of a newer generation continuous flow devices as destination therapy.[4,5] In the meantime, the approved FDA indication and CMS criteria for coverage are available.

KEY QUESTION #3. What is the range of cost-effectiveness estimates of using the FDA-approved, current generation LVAD as destination therapy in end-stage heart failure and what explains variation in these estimates?

As reported in the results for Key Question #1, we identified one randomized trial comparing a current generation continuous flow ventricular assist device (HeartMate II) to the older generation (HeartMate XVE) ventricular assist device.[1] There was also one prior trial comparing an older generation HeartMate VE device to optimal medical management.[2] There have been no studies that directly compared a current generation device to optimal medical management. We found only one analysis of cost-effectiveness that used data from these two prior trials to indirectly estimate the cost-effectiveness of using the HeartMate II ventricular assist device for destination therapy compared to optimal medical management.[35]

Rogers et al. estimated that the continuous-flow device would have an incremental cost effectiveness ratio (ICER) of $198,184 per quality-adjusted life year and $167,208 per overall life years not adjusted for in the patients' quality of life.[35] Estimates of confidence intervals around these cost-effectiveness ratios were not reported. The analysis was funded by the maker of the device and the costs were assessed from the perspective of a third-party payer, not necessarily the VA. Details of this analysis related to the key model components, source data, and the effect sensitivity analyses are summarized in Appendix D, Table 3. The ICER estimates used "base case" assumptions regarding: survival that included the 24-month estimates from the clinical trials with extrapolation of survival thereafter, costs related to the initial implantation of the ventricular assist device, costs of medical management, re-hospitalization rates and costs, device replacement costs, outpatient care costs, end-of-life costs and estimates of quality of life (utility) for each of the four NYHA classes of limitations due to symptoms of heart failure that patients may fall in after implantation of the device. The quality of life assessment did not incorporate other medical conditions including the impact of device complications. Limited sensitivity analyses that changed one model component at a time suggested that the variation in the cost-effectiveness estimates were most dependent on the extrapolated estimates of survival from 24 to 60 months and the costs of the initial implantation of the ventricular assist device and subsequent re-hospitalizations for complications. Plausible changes to any of these individual

assumptions resulted in estimates of cost-effectiveness ranging from $150,000 to $300,000 per quality-adjusted life year.

Prior analyses that compared use of the older generation ventricular assist device (HeartMate VE) to optimized medical management reported a cost-effectiveness ratio of $802,700 per quality-adjusted life year.[36] Rogers' adaptation of this model for the HeartMate II appeared to show a significant improvement in the cost-effectiveness. The main drivers of the improvement in cost-effectiveness were not well established, however, Rogers et al. state that the improvement was largely due to better survival, reductions in implant costs and better quality of life of surviving patients that received the device.[35] Nevertheless, destination therapy remains among the least cost-effective interventions covered by Medicare.[6]

Summary of Findings for Key Question #3

The estimated cost-effectiveness of using the HeartMate II as destination therapy for patients with end-stage heart failure was approximately $200,000 per quality-adjusted life year. The cost-effectiveness estimates did not drop below $150,000 even with more favorable assumptions regarding the outcomes or costs of using the HeartMate II ventricular assist device as destination therapy.

SUMMARY AND DISCUSSION

SUMMARY POINTS

- Only one good quality randomized trial of a newer generation continuous flow ventricular assist device as destination therapy has been reported to date. This study found that patients who received the HeartMate II had better survival, fewer major complications, spent less time in the hospital, and that their heart failure had substantially less adverse impact 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 FDA approved indication and CMS criteria for coverage of Medicare beneficiaries that are based on enrollment criteria used by pivotal randomized controlled clinical trials. Studies have not validated use of other preoperative variables to further refine patient selection and thereby improve patient outcomes.
- Only one industry-funded cost-effectiveness analysis has been reported to date. This analysis reported costs from a third payer perspective and found that the incremental cost effective ratio was approximately $200,000 per quality-adjusted life year compared to optimal medical management.

LIMITATIONS

At this time there is limited, but encouraging, data to support use of the FDA approved continuous flow ventricular assist device as destination therapy. Only one randomized clinical trial has been completed. Patients enrolled in the clinical trial were carefully selected thereby limiting the ability to generalize the results. Outcomes continue to improve with experience in selecting patients, surgical procedures to implant ventricular assist devices and postoperative patient care.

The reviewed literature did not identify any VA medical center that has enrolled patients in a clinical trial or the national INTERMACS registry. The number of veterans who would meet the current selection criteria for using a left ventricular assist device as destination therapy is not known. Additional data and analyses are needed to estimate the costs the Veterans Health Administration would incur to provide this highly-specialized care.

RECOMMENDATIONS FOR FUTURE RESEARCH

Additional high-quality data are needed to inform clinical practices and policies regarding the use of ventricular assist devices to treat patients with end-stage heart failure who are not eligible for a heart transplant. Investigators suggest the following recommendations regarding future research:

- **Create or participate in a registry of all Veterans that receive an LVAD as destination therapy, and support enrollment of Veterans in ongoing, randomized controlled clinical trials.**

  Given the small number of patients who have received destination therapy and the rapidly evolving devices and practices, it is imperative to learn as much as possible from patients

who undergo this procedure. All Veterans that receive destination therapy approved by the Veterans Health Administration should be entered into a national registry in a way that will allow separate analyses and comparisons of patient characteristics and outcomes. In addition, enrollment of patients into randomized controlled clinical trials should be encouraged. For example, a study comparing a third generation ventricular assist device to FDA-approved devices is currently trying to enroll up to 450 patients who, for the most part, meet current criteria for destination therapy.[25] As ventricular assist devices become more durable with fewer complications they are also being tested in patients with less severe heart failure given concerns that the operative risk of many patients who meet the current criteria for destination therapy is too high, and patients with a less dire prognosis without a device may benefit from increasingly reliable devices.[4,5] Permission to enroll patients in this study of a currently unapproved use of a newer device (HeartWare) should be considered to increase patient access to destination therapy.

- **Validate and, if necessary, update prediction models especially for early post-operative mortality.**

  Patients who die in the hospital soon after implantation of a ventricular assist device do not benefit. A validated prediction model for early/postoperative mortality could be applied to avoid high risk and costly attempts to use ventricular assist devices as destination therapy. Ideally clinical trials would be done to show that use of an outcome prediction model improves patient outcomes. This review did not find any established or proposed threshold for predicted risk of post operative mortality that would preclude use of destination therapy or generally be acceptable to patients and health care providers.

- **Develop decision aids to help providers share information about the benefits, risks and care needed when using an approved ventriclualr assist device as destination therapy and to help them make decisions that are consistent with the informed patient's values and preferences.**

  The difficult decision to employ a ventricular assist device as destination therapy typically is made when patients are in poor health and have a very limited life expectancy without the device. A number of benefits and risks need to be explained in ways patients can understand including the uncertainty inherent in the outcomes data. Patients need to understand the follow-up care that will be required. Future states of health when the patient might want the device to be turned off need to be anticipated and discussed. Decisions aids can enhance provider-patient communication and increase patients' knowledge and participation and acceptance of the decision.[37]

- **Update the cost-effectiveness model as more data become available and incorporate a probabilistic sensitivity analysis.**

  There have been large improvements in the cost-effectiveness of destination therapy during the past decade.[35,36] It will be important to keep updating the cost-effectiveness models as the devices and related procedures improve. This is particularly important for the model parameters that appear to be most influential i.e., long-term survival both on the device and with optimal medical management, cost of the device, cost of initial hospitalization, rehospitalization

rate and utility estimates based on measures of health-related quality of life. Additionally, adding probabilistic sensitivity modeling would help decision makers better understand the uncertainty of the estimates in the model by estimating confidence intervals around the incremental cost-effectiveness estimates. This can be done by using distributions of the model parameters with Monte Carlo simulation to assess the probability the incremental cost effectieness ratio will be less than or greater than various dollar amounts. Probabilistic sensitivity analyses that took the UK National Health Service payer perspective have been completed for the cost-effectiveness of continous flow LVAD as a bridge to transplant providing a good example of what could be done for destination therapy.[38]

- **Conduct a budget impact analysis.**

  Cost-effectiveness analyses provide general estimates from a societal perspective or the perspective of a generic third party payer, however, additional budget impact analyses would be useful to help the Veterans Health Administration understand the potential impact of different strategies and policies for providing destination therapy. For example, it would be important to know how many veterans would be eligible and interested in the treatment and what the options would be in terms of how and where this therapy would be provided.

CONCLUSIONS

Key Question #1

Use of the FDA-approved HeartMate II rather than the HeartMate XVE left ventricular assist device results in superior patient outcomes (better survival and daily existence, fewer harmful complications). [moderate strength evidence]

Key Question #2

Preoperative correlates of patient outcomes have not been established as patient selection criteria that can lead to better patient outcomes. [insufficient evidence]

Key Question #3

The cost-effectiveness of HeartMate II ventricular assist device for destination therapy has been estimated to be approximately $200,000 per quality-adjusted life year when compared to optimal medical management. [low strength evidence]

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APPENDIX A. TECHNICAL EXPERT PANEL MEMBERS

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