APPENDIX A. TECHNICAL EXPERT PANEL MEMBERS

Inder Anand, MD, FRCP, DPhil
Director, Heart Failure Program
University of Minnesota Medical School

William Gunnar, MD, JD
National Director of Surgery
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William Holman, MD
Chief, Surgical Services
Birmingham VA Medical Center

Gundars Katlaps, MD
Chief, Section of Cardiothoracic Surgery
Surgical Director, Programs of Heart Transplantation and Mechanical Assist Devices
Richmond McGuire VA Medical Center

Richard Schofield, MD, FACC
Chairman of Medicine
Malcolm Randal VA Medical Center
Chief, Medical Service
North Florida/South Georgia Veterans Health System

Josef Stehlik, MD
Director, VAMC Cardiac Transplant Program
VA Salt Lake City Health Care System

APPENDIX B. SEARCH STRATEGY

Database: Ovid MEDLINE(R) <1948 to October Week 3 2011>

Search Strategy:

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1 exp Heart-Assist Devices/ or lvad.mp.
2 ventric$ assist.mp.
3 artificial ventricle.mp.
4 heartware.mp.
5 heartmate.mp.
6 novacor.mp.
7 coraide.mp.
8 lionheart.mp.
9 or/1-8
10 limit 9 to (english language and humans and yr="1995 -Current")
11 congestive heart failure.mp. or exp Heart Failure/ or cardiac failure.mp. or myocardial failure.mp. or ventricular dysfunction.mp. or exp Ventricular Dysfunction/
12 10 and 11
13 limit 12 to (case reports or comment or editorial or letter)
14 12 not 13

APPENDIX C. PEER REVIEW COMMENTS/AUTHOR RESPONSES

REVIEWER COMMENT	RESPONSE
1. Are the objectives, scope, and methods for this review clearly described?	
Yes. This is a very well written report that reviewing the evidence available for the use of the current generation of left ventricular assist devices as destination therapy. Given the very limited published data on the subject, the authors have adequately addressed the three key questions required for this topic.	
Yes	
Yes	
Yes. The methods are clearly described and are standard for this type of evaluation. However, it should be noted that there are factors inherent in ventricular assist devices (VADs) that importantly influence their evaluation in clinical trials. First, the control group in trials to date (e.g. optimal medical management group of the REMATCH trial) is critically ill. Survival of the control group in REMATCH was so poor that a medical control group will be considered ethically unacceptable for subsequent trials, unless the trial specifically examines less ill patients (e.g. the The Evaluation of VAD InterVEntion Before Inotropic Therapy [REVIVE-IT] trial cited in the report, which will examine class IIIB patients). The REVIVE-IT trial itself faces challenges with regard to patients that cross-over from medical to device management during the trial. Clinical trials of new VADs for class IV heart failure will use approved devices as the control group. The report recognizes this situation and its limitations. A second factor stems from the fact that the therapy cannot be blinded to the observers or the patient. The use of objective measures such as maximal oxygen consumption and six minute walk test is therefore particularly important to trials and their evaluation	We have added a statement about use of more objective endpoints to the section on page 11 about patient outcomes for KQ1. We believe that although more objective endpoints such as exercise tests would be useful given the inability to blind comparisons between devices and non-surgical medical therapy, it is very difficult to translate changes in maximal exercise test parameters to effects on patients' lives. Subjective patient outcomes could be less of an issue in unblinded comparisons of devices.
Yes	
Yes. I found this review to be well-written and focused. The objectives of the review were clearly defined, and were presented in logical and concise manner. The scope of the review was also well described and took proper account for lack of sufficient data to definitively answer one of the key points. The methods applied to the project were reasonable and consistent with evidence-based analysis of the data.	
Yes. Objectives, scope and methods are clearly described and appropriate for the potential therapy being evaluated.	
2. Is there any indication of bias in our synthesis of the evidence?	
No	
No	
No	
No	
No	
No. I could not perceive a detectable bias in the synthesis of the evidence. The authors are to be commended for a balanced approach to the key questions posed	
No. Evaluation appears to be free of any bias and the Technical Expert Panel Members are noted experts capable of providing appropriate guidance and oversight	

REVIEWER COMMENT	RESPONSE
3. Are there any published or unpublished studies that we may have overlooked?	
Yes. The authors have reviewed most of the published and unpublished data on the subject from 1995 to October 2011. However, it would be useful to include in this document the additional information in the latest Quarterly Statistical Report from the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) available on their web site. According to this report, the total number of medical centers performing LVAD implantations for destination therapy have doubled from 69 to 135 as quoted by the authors (page 7, para 3, line 6). Moreover, over a fifth of all LVADs have been implanted for destination therapy.	Updated information from the fourth annual INTERMACS report has been added to the Registry section on page 7. In addition, the INTERMACS website is now referenced there to provide access to up-to-date information.
No. There are limited publications related to HeartMate II	
No	
Yes. The fourth INTERMACS report was published in the February issue of the Journal of Heart and Lung Transplantation. The information will not dramatically change the findings of the VA-ESP report, in my opinion. However, the report may want to include the citation. The HeartWare left ventricular assist device is currently under review by the FDA for the bridge-to-transplantation indication. It may be worth mentioning this device as a future consideration, primarily due to the pump's small size. It was chosen for the REVIVE-IT trial.	Updated information from the fourth annual INTERMACS report has been added to the Registry section on page 7. In addition, the INTERMACS website is now referenced to provide access to up to date information. We have now mentioned the HeartWare by name when discussing ongoing studies on pages 3, 17 and 23.
Yes 1) Ann Thorac Surg. 2011 Nov;92(5):1593-9; discussion 1599-600. Epub 2011 Oct 31. **Lessons learned from experience with over 100 consecutive HeartMate II left ventricular assist devices.** John R, Kamdar F, Eckman P, Colvin-Adams M, Boyle A, Shumway S, Joyce L, Liao K. 2) J Heart Lung Transplant. 2011 Aug;30(8):849-53. Epub 2011 Apr 29. **Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device.** Demirozu ZT, Radovancevic R, Hochman LF, Gregoric ID, Letsou GV, Kar B, Bogaev RC, Frazier OH. 3) J Heart Lung Transplant. 2012 Jan;31(1):1-8. Epub 2011 Oct 8. **Pre-operative and post-operative risk factors associated with neurologic complications in patients with advanced heart failure supported by a left ventricular assist device.** Kato TS, Schulze PC, Yang J, Chan E, Shahzad K, Takayama H, Uriel N, Jorde U, Farr M, Naka Y, Mancini D. 4) Ann Thorac Surg. 2010 Oct;90(4):1270-7. **Infectious complications in patients with left ventricular assist device: etiology and outcomes in the continuous-flow era.** Topkara VK, Kondareddy S, Malik F, Wang IW, Mann DL, Ewald GA, Moazami N.	The first report listed was screened but not included in this review because only 17 out of the 130 cases were destination therapy. The second report listed was screened but not included this review because most cases were not destination therapy. The article does point out the need to consider the risk and incidence of gastrointestinal bleeding as an important patient outcome particularly with continuous flow devices. Information about this important patient outcome was extracted whenever it was reported by studies that were included in the review. The third report listed was published after the literature search was done. It was not included this review because most cases used the older pulsatile flow HeartMate device that has become obsolete. Furthermore, the report doesn't provide enough information to determine the predictive accuracy of identified risk factors for neurological complications. Judging by the magnitude of the differences, most likely the identified risk factors will not turn out to provide adequate discrimination. The article does point out the need to consider the risk and incidence of neurological complications as an important patient outcome. Information about this important patient outcome was extracted whenever it was reported by studies that were included in the review. The fourth report listed was screened but not included this review because most cases weren't destination therapy, and the report doesn't provide much information about patient selection based on the risk of infectious complications. The article does point out the need to consider the risk and incidence of infectious complications as an important patient outcome. Information about this important patient outcome was extracted whenever it was reported by studies that were included in the review.

REVIEWER COMMENT	RESPONSE
Yes. The authors may wish to review the following citation: "Moreno SG, Novielli N, Cooper NJ. Cost-effectiveness of the implantable left ventricular assist device HeartMate II for patients awaiting heart transplantation. J Heart Lung Transplant March 2012 (e-published ahead of print)", and the accompanying editorial by MS Slaughter and JG Rogers, titled "Determining the cost-effectiveness of mechanical circulatory support"	We have carefully reviewed both of these citations and decided against adding this cost-effectiveness analysis to the results section of the report because it took a UK National Health Service payer perspective and only looked at LVAD use as a bridge to heart transplant, However, the Moreno 2012 article does provide a good example of what could be done in a future in terms of a probabilistic cost-effectiveness analysis, so we incorporated information about this study into the Recommendations for Future Research Section on page 24.
No. There are no significant publications that have been overlooked or additional publications not included that would add value to the evaluation of in any way change the conclusions that have been made.	
4. Additional suggestions or comments	
Minor comments: Page 4 bullet # 3, line3; correct "ventricular" Page 35, column 4; it is unclear for which comparison the HR for all –cause death within 30 days refers to? Page 37, column 4; Mean pulmonary pressure > or ≤ 25 mmHg?	Typographical error on page 4 corrected. The reference groups for the HR's now have been noted. The article repeatedly states ≤ 25 as indicated. The authors considered a low mean pulmonary artery pressure to be an indicator of right heart failure although others have associated worse outcomes with higher pulmonary pressures that can precipitate right heart failure after implantation of a left ventricular assist device.
On page 23 you state "A consensus of health care providers and patients needs to be established for the level of predicted mortality that would generally preclude use of destination therapy." Ideally, this would be based on data from randomized trials directly. Estimating the risk benefit of a VAD on sub-populations without trial data has a high potential for error. If economic studies determine a minimum survival threshold that must be achieved in order for VAD implantation to be cost-effective then it would be useful to develop studies to predict survival less than that threshold. For your recommendation to register patients I would state the name/details of registry as many will not read the text to figure out what you are talking about. They may assume you are suggesting the VA could/ should start its own registry.	We agree and have revised the statement on page 23 to, "Ideally clinical trials would be done to show that use of a prediction model improves patient outcomes. This review did not find any established or proposed threshold for predicted risk that would preclude use of destination therapy or generally be acceptable to patients and health care providers." The INTERMACS registry has now been specified.
The report was well written with appropriate supporting literature. With regard to Key Question #2, information from INTERMACS defines risk factors for death following implantation of a ventricular assist device. At this point in time, the information has not been reduced to a quantitative predictive nomogram, but probably will be in the near future. Dr. David Naftel at UAB can give the group a better estimation of the timeline for developing a system to predict outcome in mechanical circulatory assist patients. I have no additional comments or suggestions	

REVIEWER COMMENT	RESPONSE
I've added several references describing outcomes AFTER the clinical studies were concluded. You can see that outcomes are not as good for patients getting devices WITHOUT being enrolled in clinical studies. This is not an observation unique to this particular clinical problem, but I think it warrants more attention. I noticed that the comparison focused on the comparison of newer devices to older ones, based on the assumption that LVAD's generally have been shown to improve survival v. nonsurgical management. But what about other outcomes? There is an alarming incidence of disabling strokes in patients with LVAD's. How would this figure in a patient's decision to have an LVAD implanted? Would patient's be willing to accept a higher mortality with nonsurgical management in order to avoid the increased likelihood of a disabling stroke if an LVAD is implanted? (For this reason, issues of informed consent also warrant attention. Are patients being made aware of the high complication rates before agreeing to implantation? (I appreciate this was not part of the charge of the committee.)	Points well taken. Observational studies that directly compared outcomes in practice versus clinical trials were of interest as were reports of patient outcomes in case series. Many of these reports were from investigational sites and we couldn't always tell if the report included or excluded patients that were enrolled in clinical trials. Hopefully, the INTERMACS registry data will provide better estimates of the incidences of all types of patient outcomes. The articles did not identify any additional patient outcomes that were not considered during the review.
Regarding Key Question 1, there is no debate that use of the HeartMate II LVAD as compared to the HeartMate XVE LVAD in appropriate candidates leads to better outcomes, and that if compared to medical therapy alone the outcomes would be more decidedly favorable. However it would be important for the reviewers to point out that overall survival for DT patients with a HeartMate II was still only 55% at 2 years. This point would be of relevance to readers of the review and to policy makers. It is possible, perhaps even likely, that subsequent registry data will show improvement in the 2 year survival for DT patients supported via HeartMate II devices. If future updates to this report are generated, such data would be of considerable importance and should be disseminated. I am aware of anecdotes reporting very high 1 year survival rates for DT LVAD patients (I believe from the INTERMACS data set) but to my knowledge these data are not yet published. Are there data regarding readmission rates for patients who have undergone DT LVAD implantation? Such data would also be of interest to VA leadership. High rates of readmission post-operatively could mitigate some of the otherwise considerable advantages of LVAD placement in this very ill population of patients. I am aware of anecdotal reports that LVAD patients average >5 hospital readmissions over the first postoperative year, but these are purely anecdotes. Data in this regard might be useful. I would agree with the authors that any patient who receives a DT LVAD via the Veterans Administration should be put into a robust data registry and that patient outcomes should be followed over time. I would submit that these patients perhaps should be entered into the VA surgical quality improvement database, which is strong and robust and already is established at every VA hospital with a surgical program on site. I would also consider whether current LVADs being placed by the VA as bridge to transplant should also be entered into a clinical database in order to track outcomes. On page 7, paragraph 1 of the report, the authors note criteria established by the Centers for Medicare and Medicaid Services for clinical centers planning to initiate a DT LVAD program. The criteria included participation in a data registry, minimum volume standards for the implanting surgeon, and facility disease-specific certification for VADs by The Joint Commission. While VA would probably not be compelled to follow such CMS guidelines, one wonders whether it would nevertheless be wise and prudent to do so both to insure quality of the program and to deflect external criticism which might be directed at the VA for undertaking such a complex endeavor.	The outcomes of using the HeartMate II as destination therapy study including the overall survival are summarized in the Executive Summary (page 3) and in the body of the report and evidence table. We have also cited other survival estimates in the report and added updated 2-year estimates from the INTERMACS registry on page 17. All estimates appear to be remarkably consistent with a trend to improved survival as patient selection and processes improve. Our search did not find good estimates of readmission rates or what complications caused them. The cost effectiveness estimates do include readmission rates of 0.21 per month for device therapy versus 0.13 for medical therapy, and the cost effectiveness ratio was sensitive to the presumed readmission rate as has been pointed out in the report. The VA surgical quality improvement data base has been added to the recommendation. We agree, and had summarized the CMS criteria and other guidelines in the report to facilitate consideration by VA policymakers.

REVIEWER COMMENT	RESPONSE
My only additional comment would pertain to Key Question #2 regarding site characteristics associated with patient benefits or harm. There is a trend in the U.S for "non-transplant" centers to establish stand-alone LVAD DT programs. It is unclear if these programs that have minimal to no transplant experience and have little to no experience with implanting LVADs as BTT will have similar outcomes in an older and potentially sicker DT patient population. It is possible that the VA system will need to address the question of whether it is feasible, makes clinical or economic sense to allow a LVAD DT program in a VA hospital without an advanced heart failure program that includes experience and expertise in the evaluation of heart transplant patients. Hopefully there will be some data in the next 3 – 5 years to help resolve this issue.	
5. Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.	
Provide emphasis regarding how remarkable technologic advancements have resulted in improved device outcomes. CMS did not consider conditional reimbursement until after the Slaughter study was published.	
No changes are needed.	
I think that the report accurately depicts the status quo of mechanical circulatory support. The Joint Commission has a process for accrediting mechanical circulatory support programs that may be of interest to the Veterans Administration. The requirements for this specialized accreditation describe in detail the personnel, processes, and infra-structure that are required for a mechanical circulatory support program	
The authors are to be congratulated for creation of a balanced, thoughtful and well written report.	
No additional recommendations	

APPENDIX D. EVIDENCE TABLES

Table 1. Key Question #1: Effects on Patient Outcomes

Study/Country/ Funding Source	Inclusion/Exclusion Criteria	Baseline Characteristics	Comparison	Patient Outcomes	Study Quality
Slaughter 2009[1] **38 centers in U.S.** **Funding Source: Manufacturer Thoratec**	Inclusion Criteria: Ineligible for heart transplant Refractory to optimal medical care Left ventricular ejection fraction <25% Peak oxygen consumption <14ml/kg/min if able to exercise NYHA class IIIb or IV symptoms for 45 out of last 60 days, or IABP for 7 days, or intravenous inotrope for 14 days Exclusion Criteria: Inordinately high surgical risk Body mass index > 40 kg/m^2 Previous heart transplant Psychiatric condition or otherwise impaired protocol compliance Severe respiratory disease Serum creatinine ≥ 3.5 mg% or chronic dialysis Any other condition that could limit survival to < 3 years Several others not listed here	n = 200 Mean Age (yr): 62 Male: 84% White: 74% Mean LVEF: 17% IV inotrope: 79% IABP: 22% Mech. Vent.: 8% ICD: 82% CRT: 60% NYHA class: III - 22% IV - 69%	Investigational (I): HeartMate II continuous flow LVAD with warfarin (n=134) (1 received the control LVAD) Control (C): HeartMate XVE pulsatile flow LVAD without warfarin (n=66) (3 received the investigational LVAD) Median time on LVAD: I – 1.7 years C – 0.6 years	Primary composite endpoint of survival free of disabling stroke or reoperation to remove device including urgent heart transplant at 24 months I – 46% vs C – 11% (p<0.001) HR = 0.38 (95% CI 0.27 to 0.54) First events: Death I - 33% vs C - 41% (p=0.05) HR = 0.59 (95% CI 0.35 to 0.99) Device Removed I - 10% vs C - 36% (p<0.001) HR = 0.18 (95% CI 0.09 to 0.37) Disabling Stroke I - 11% vs C - 12% (p=0.56) HR = 0.78 (95% CI 0.33 to .82) As treated actuarial 1 and 2 year survival estimates ignoring device replacements (overall p=0.008 with HR = 0.54 (95% CI 0.34 to 0.86)) I (n=133): 68% (1 year) and 58% (2 year) C (n=59): 55% (1 year) and 24% (2 year) % of follow-up time spent as outpatient I – 88% vs C – 74% (p=0.02) Median initial length of stay I – 27 vs C – 28 days Readmission rate (per person year) I – 2.6 vs C – 4.2 (p=0.02)	Randomized Groups similar at baseline with no need for further adjustment Not blinded Withdrawals explained Intention to Treat (ITT) analysis of primary outcome; other outcomes analyzed as treated Adequate number and precision of estimates

Study/Country/ Funding Source	Inclusion/Exclusion Criteria	Baseline Characteristics	Comparison	Patient Outcomes	Study Quality
Slaughter 2009[1] **Continued**	See above	See above	See above	NYHA class I /II among survivors at 1-year I (n=72) - 76% vs C (n=18) - 61%) (p=0.22) Mean LHFQ Score among survivors at 1-year (lower better) I (n=76) - 34 vs C (n=19) - 44 (p=0.03) Mean KCCQ Clinical Score among survivors at 1-year (higher better) I (n=76) - 69 vs C (n=18) - 61 (p=0.12) Selected Adverse Event Rates (per person yr) I C p-value Stroke 0.1 0.5 <0.001 Sepsis 0.4 1.1 <0.001 Major bleed 1.6 2.4 0.06 Right heart failure 0.1 0.5 <0.001 Respiratory failure 0.3 0.8 <0.001 Cardiac arrhythmia requiring treatment 0.7 1.3 0.006 Renal failure 0.1 0.3 <0.001	See above

Study/Country/ Funding Source	Inclusion/Exclusion Criteria	Baseline Characteristics	Comparison	Patient Outcomes	Study Quality
Park 2012[23] 38 centers in U.S. Funding Source: Manufacturer Thoratec	Continued access protocol with same inclusion/exclusion criteria as previous study (Slaughter 2009[1])	n = 414 Mean Age (yr): 63 Male: 79% Mean LVEF: 17% IV inotrope: 78% IABP: 20% Mech. Vent.: 5% ICD: 83% CRT: 61% NYHA class: III - 34% IV - 66% Predicted 1-year survival without device: 41%	<u>All received HeartMate II</u> Early enrollees (EE) in RCT from 3/2005 to 5/2007 (n=133), reported previously Later enrollees (LE) in non-randomized continued access protocol from 5/2007 to 3/2009 (n=281) Median duration of device use: EE 1.7 vs LE 2.1 yrs	<u>Primary composite endpoint</u> - survival free of disabling stroke or reoperation to remove device including urgent heart transplant at 24 months EE – 50% vs LE – 59% (p=0.07) <u>Actuarial 1 and 2 year survival</u> EE: 68% (1 year) and 58% (2 year) LE: 73% (1 year) and 63% (2 year) overall p=0.21 <u>Median initial length of stay</u> EE – 27 vs LE – 23 days (p=0.09) <u>Readmission rate (per person year)</u> I – 2.6 vs C – 4.2 (p=0.02) <u>NYHA class I or II among survivors at 1-year</u> EE (n=73) - 77% vs LE (n=161) - 77% <u>Mean LHFQ Score among survivors at 6-months(lower better)</u> EE (n=86) - 30 vs LE (n=184) - 38 over 2 years p=0.04 <u>Mean overall KCCQ Score among survivors at 6-months (higher better)</u> EE (n=86) - 64 vs LE (n=187) - 70 over 2 years p=0.08 <u>Selected Adverse Event Rates (per person yr)</u> EE LE p-value Ischemic stroke 0.06 0.05 0.48 Hemorr. stroke 0.07 0.03 0.01 Sepsis 0.38 0.27 0.02 Device infection 0.47 0.27 <0.001 Major bleed 1.89 1.27 <0.01 Right heart failure 0.16 0.13 0.39 Cardiac arrhythmia requiring treatment 0.69 0.46 <0.01 Renal failure 0.10 0.06 0.11 Pump replacement 0.06 0.04 0.35	Not randomized Groups similar at baseline with no need for further adjustment Not blinded Withdrawals not explained Intention to Treat (ITT) analysis Adequate number and precision of estimates

Study/Country/ Funding Source	Inclusion/Exclusion Criteria	Baseline Characteristics	Comparison	Patient Outcomes	Study Quality
Kirklin 2011[3] 3rd INTERMACS Annual Report 69 centers in United States Funding Source: NHLBI	Registered cases of destination therapy	n=385 Mean Age (yr): 62 Male: 84% White: 76% Contraindications for Heart Transplant Age: 33% Renal: 22% Obesity: 16% Pulmonary: 20% Preop Profile: Shock: 9% Declining: 41% Inotrope: 26% Recurrent: 15%	HeartMate II (HMII) continuous flow LVAD (n=281) HeartMate XVE (HMXVE) pulsatile flow LVAD (n=104)	Actuarial Survival HMII HMXVE Month 3 86% 83% Month 6 81% 70% Month 12 74% 61% Month 24 na 39% p=0.02 (censored at transplant or device removal)	Not Randomized Baseline similarity not reported Different time periods No adjustments Not blinded Losses to follow-up not reported Intention to Treat (ITT) analysis Adequate number and precision of estimates
Strüber 2008[24] 12 centers in Europe Funding Source: Not reported	Consecutive cases; selection of patients for destination therapy not described	n= 31 Mean age (yr): 52 Otherwise not described	HeartMate II continuous flow LVAD used as destination therapy No control group	80% 3-month survival 71% 6-month survival 71% 1-year survival Other outcomes not reported for destination therapy subgroup	Small retrospective unblinded case series without a control group or description of baseline characteristics or follow-up

NYHA - New York Heart Association, IABP – intra-aortic balloon pump, IV – intravenous, ICD - implanted cardiac defibrillator, CRT - cardiac resynchronization therapy, LVAD - left ventricular assist device, HR – hazard ratio, CI - confidence interval, LHFQ - Minnesota Living with Heart Failure Questionnaire with lower scores indicating the patients perceived less adverse effects of heart failure on their quality of life, KCCQ - Kansas City Cardiomyopathy Questionnaire - the clinical score is a measure of physical function and heart failure symptoms with higher scores indicating less symptoms and better function

Table 2. Key Question #2: Patient Selection

Study/Country/ Funding Source	Inclusion/Exclusion Criteria	Sample of Patients	Outcomes & Baseline Correlates	Study Quality
Kirklin 2011[3] **69 centers in U.S.** **Funding Source: NIH, others**	Inclusion Criteria: Case registered in INTERMACS FDA-approved ventricular assist device implanted as destination therapy from June, 2006 to September 2010	n = 385 HeartMate II (n=281, 73%) HeartMate XVE (n=104, 27%) Mean Age (yr): 62 Male: 84% White: 76% Black: 18% INTERMACS CLASSIFICATION Cardiogenic shock: 9% Progressive decline: 41% Inotrope dependent: 26% Recurrent decompensated heart failure: 15% Greatly limited exertion: 7% Class IIIb: 2% REASONS NOT ELIGIBLE FOR HEART TRANSPLANT Advanced age: 33% Renal dysfunction: 22% High body mass index: 16% Pulmonary hypertension: 12% Other: 17%	Unspecified number and names of variables tested; reference groups for HR's are the complements of those described 1) All-cause death within 30 days, n=35 a) cardiogenic shock HR = 3.5, p<0.01 b) need for concomitant surgery HR = 3.0, p=0.02 c) 10 units higher BUN HR = 1.3, p=0.001 2) All-cause deaths after 30 days, n=62 a) HeartMate XVE vs HeartMate II HR = 2.75, p=0.002 interactions with other predictors not reported b) pulmonary hypertension HR = 3.6, p=0.0001 c) 10 units lower sodium HR = 2.1, p=0.005 d) diabetes HR = 2.0, p=0.01 e) age 70 vs 60 years HR = 1.8, p<0.0001	Patients eligible for destination therapy, but not all received HeartMate II Most variables assessed before implantation surgery Measurements of potential predictors not standardized or described Presumably complete follow-up of deaths Most predicted probabilities and confidence intervals not reported, no calibration or validation of prediction model No assessment of whether or how much use of variables could improve patient selection or outcomes
Levy 2009[33] **20 centers in U.S.** **Funding Source: Thoratec Corp**	Inclusion Criteria Participants in clinical trial of HeartMate VE for destination therapy compared to optimal medical therapy (REMATCH Study)	n=129 (some missing values needed for the prediction model were imputed and use of inotropes or an intra-aortic balloon pump and/or ventilator were added to the prediction model) n= 61 in medical therapy arm Mean Age (yr): 67 Male: 80% Mean LVEF: 17% NYHA class IV: 100% IV inotrope: 56% Intra-aortic balloon pump: 8% Defibrillator: 35%	Survival predictions made using variables in the Seattle Heart Failure Model Average estimated 1-YEAR SURVIVAL in medical therapy arm (n= 37 deaths) 30% vs 28% observed 81% had < 50% estimated 1-year survival Note: guidelines for destination therapy recommend patient's expected 1-year survival be < 50% Interaction between treatment effect (assist device versus medical therapy) and Seattle Heart Failure Score was not significant (p=0.86)	Patients eligible for destination therapy, but none received HeartMate II Variables assessed before implantation surgery Measurements of potential predictors not standardized or described Complete follow-up for deaths No confidence intervals on predicted probabilities in small groups, a little information about calibration and validity of predictions Little assessment of whether or how much use of variables could improve patient selection or outcomes No evidence risk score discriminates groups of patients that do or do not have a survival benefit

Study/Country/ Funding Source	Inclusion/Exclusion Criteria	Sample of Patients	Outcomes & Baseline Correlates	Study Quality
Lietz 2007[11] **56 centers in U.S.** **Funding Source: not reported**	Inclusion Criteria Use of HeartMate XVE for destination therapy after FDA approval, November 2002 – 2005 Consent to be in manufacturer's case registry 280/309 (91%)	n= 280 (222 with complete data for analysis of in-hospital mortality) Mean Age (yr): 61 Male: 82% Mean LVEF: 18% IV inotrope: 70% NYHA class IV: 100%	Numerous variables examined by stepwise logistic regression including demographics and body size, cause of heart failure, history of cardiovascular diseases, other comorbidities, medical and device therapy for heart failure, hemodynamics, laboratory data, year and center experience. Regression estimates used to calculate individual risk score. 90-DAY IN-HOSPITAL MORTALITY, n=60 (27%) CAUSES Sepsis - 33% Multiorgan failure - 20% Right heart failure - 14% Respiratory failure - 7% Technical difficulties - 5% Device failure - 5% Hemorrhage - 3% Stroke - 3% Several other causes - 10% INDEPENDENT CORRELATES (OR = odds ratio) Platelet count ≤ 148,000; OR = 7.7 Serum albumin ≤ 3.3 g/dl; OR = 5.7 INR > 1.1; OR = 5.4 Vasodilator; OR = 5.2 Mean pulmonary artery pressure ≤ 25 mmHg; OR = 4.1 Aspartate aminotransferase > 45 U/ml; OR = 2.6 Hematocrit ≤ 34%; OR = 3.0 Blood urea nitrogen > 51 U/dl; OR = 2.9 No IV inotrope; OR = 2.9	Patients eligible for destination therapy, but none received HeartMate II Variables assessed before implantation surgery Measurements of potential predictors not standardized or described Presumably complete follow-up of in-hospital deaths Wide confidence intervals on predicted probabilities, calibration questionable, and predictions not validated No assessment of whether or how much use of variables could improve patient selection or outcomes; thresholds of acceptable operative risk not defined

Study/Country/ Funding Source	Inclusion/Exclusion Criteria	Sample of Patients	Outcomes & Baseline Correlates	Study Quality
Leitz 2007[11] **Continued**	See above	See above	RISK SCORE C-statistic 0.89 RISK SCORE CATEGORIES % PREDICTED (CI) vs OBS 0 to 8 (n=65) 2 (1 to 5) vs 6 9 to 16 (n=111) 12 (8 to 18) vs 14 17 to 19 (n=28) 44 (33 to 56) vs 61 >19 (n=18) 81 (66 to 91) vs 82	See above
Adamson 2011[34] **Single center in U.S.** **Funding Source: not reported**	Inclusion Criteria Patients enrolled in clinical trials of the HeartMate II ventricular assist device All carefully screened using criteria of clinical trials and CMS	n=55 subgrouped into < 70 (n= 25) and ≥ 70 years old (n=30) Male: not reported NYHA class IV: 100% Mean LVEF: 20% IV inotrope: 64% Intra-aortic balloon pump: 5% Defibrillator: 74% Cardiac resynchronization therapy: 51% Mean Destination Therapy Risk Score: 9.3	**< 70 group** **≥70 group** MEAN AGE (years) 57 76 MEDIAN DURATION WITH DEVICE (days) 415 482 DROPOUTS 3 0 SURVIVAL (p=0.81) 30 days 96% 97% 6 months 88% 83% 12 months 72% 75% AT 6 MONTHS NYHA CLASS I or II 100% 89% p=0.35 MEAN IMPROVE in MLHFQ SCORE 36 42 p=0.07 MEAN IMPROVE in KCCQ SCORE 32 42 p=0.88 ADVERSE EVENT RATES No significant differences Major Bleeding 28% 30% Sepsis 24% 20% Device-related infect. 20% 17% Cardiac Arrhythmia 32% 33% Stroke 8% 10% Right heart failure 4% 3% Renal failure 4% 3%	Patients eligible for destination therapy, received HeartMate II Age determined before implantation surgery and likely valid Presumably complete follow-up in trials No confidence intervals on differences between small age subgroups No adjustment for preoperative differences

INTERMACS – Interagency Registry for Mechanically Assisted Circulatory Support, LVEF – left ventricular ejection fraction, IV – intravenous, NYHA – New York Heart Association, HR – hazard ratio, OR – odds ratio, INR – international normalization ratio, CI – 95% confidence interval, OBS – observed, BUN – blood urea nitrogen, MLHFQ – Minnesota Living with Heart Failure Score, KCCQ – Kansas City Cardiomyopathy Questionnaire

Table 3. Key Question #3: Cost-effectiveness

Study/Design/ Funding Source	Key Model Components and Source	Base Case	Sensitivity Analyses	Range in ICER per QALY*	Study Limitations
Rogers 2012[35]	24-mo survival for LVAD[1]	KM curve	NA	NA	The data regarding the difference in the effect of LVAD vs. OMM involves an indirect comparison across 2 RCTs
	24-mo survival for OMM[2]	KM curve	NA	NA	
Cost-effectiveness analysis of continuous-flow LVAD versus OMM using a Markov model	Long-term survival extrapolation for LVAD	Exponential	Linear, Stop and drop	$180,000-$375,000	
	Long-term survival extrapolation for OMM[3]	Exponential	NA	NA	
	LVAD implantation hospital cost[4]	$193,812	$122,785–$264,839	$150,000-$250,000	The long-term outcome data are extrapolated from 2 years of RCT data
	LVAD implantation professional service cost[5]	$8,841	NA	NA	
	LVAD replacement cost[6]	$131,430	NA	NA	All sensitivity analyses only varied one parameter at a time, whereas a probabilistic model that allows multiple parameters to vary at the same time might more accurately assess the overall uncertainty in the model
	Monthly LVAD replacement rate [1]	0.005	NA	NA	
Funding Source: Thoratec Corp	Rehospitalization cost (per event)[7,8]	$6,850	$6,850–$30,627	$200,000-$280,000	
	Monthly rehospitalization rate for LVAD[1]	0.21	NA	NA	
	Monthly rehospitalization rate for OMM[7]	0.1325	0.1325-0.26	$195,000-$200,000	
	Monthly outpatient costs[9,10]	$2,331	NA	NA	
	End-of-life cost[11]	$44,211	NA	NA	
	Utility for NYHA Class I[12]	0.855	0.641-1.0	$180,000-$230,000	Utilities used to calculate quality-adjusted life years were based on NYHA classes
	Utility for NYHA Class II[12]	0.771	0.578-0.964	$175,000-$225,000	
	Utility for NYHA Class III[12]	0.673	0.505-0.841	$190,000-$205,000	
	Utility for NYHA Class IV[12]	0.532	0.399-0.665	$190,000-$200,000	

LVAD - left ventricular assist device, OMM - optimal medical management, NYHA - New York Heart Association, RCT – randomized controlled trial, ICER- incremental cost-effectiveness ratio, QALY- quality adjusted life year

*This is the range in Incremental Cost Effectiveness Ratio per Quality Adjusted Life Year when the model is varied over the range of values in the sensitivity analysis. The values were roughly estimated to approximately the nearest $5,000 using Figure 3 from Rogers et al., 2012.[35]

Table 3. Reference List

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(5) Centers for Medicare and Medicaid Services.Standard Analytic File, 2008. Centers for Medicare and Medicaid Services, Baltimore, MD.

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(12) Gohler A, Geisler BP, Manne JM, Kosiborod M, Zhang Z, Weintraub WS et al. Utility estimates for decision-analytic modeling in chronic heart failure--health states based on New York Heart Association classes and number of rehospitalizations. *Value Health* 2009;12(1):185-7.