QUERI

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

EXECUTIVE SUMMARY

May 2012

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research & Development Service
Washington, DC 20420

Prepared by:
Evidence-based Synthesis Program (ESP) Center
Minneapolis VA Medical Center
Minneapolis, MN
Timothy J. Wilt, M.D., M.P.H., Director

Investigators:
Principal Investigators:
Thomas S. Rector, Ph.D.
Brent C. Taylor, Ph.D., M.P.H.

Research Associates:
Nancy Greer, Ph.D.
Indulis Rutks, B.S.

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.

Recommended citation: Rector TS, Taylor BC, Greer N, Rutks I, and Wilt TJ. Use of Left Ventricular Assist Devices as Destination Therapy in End-Stage Congestive Heart Failure: A Systematic Review. VA-ESP Project #09-009; 2012.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the Minneapolis VA Medical Center, Minneapolis, MN funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

EXECUTIVE SUMMARY

BACKGROUND

Heart failure is defined as reduced ability of the heart to pump blood and maintain normal bodily function. Heart transplantation is currently the preferred treatment for end-stage heart failure but the supply of donor hearts is insufficient to meet the need and many patients are not eligible for transplantation due to age or comorbid conditions.

Implantable mechanical pumps can assist the circulation of blood by the ventricles. Left ventricular assist devices (LVADs) have been approved by the U.S. Food and Drug Administration (FDA) for use in patients awaiting transplant (a bridge to transplant) and as a last resort in patients with refractory heart failure who are not eligible for a heart transplant (destination therapy). In January 2010, the first newer generation, rotary continuous flow ventricular assist device (HeartMate II) was approved by the FDA for destination therapy. Eligibility criteria are essentially the same as those used to select patients for the pivotal clinical trial that included patients with shortness of breath and/or fatigue at rest or during minimal exertion despite treatment with optimal therapy for heart failure associated with a low ejection fraction (< 25%) who were not candidates for heart transplantation due to their age or co-morbid conditions. The purpose of this report is to review the scientific evidence for use of the current generation of left ventricular assist devices as destination therapy.

The 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?

METHODS

We searched MEDLINE using standard search terms (Appendix B). The search was limited to articles involving human subjects and published in the English language from 1995 to October 2011. We also searched 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. Reference lists of articles and reports were reviewed to identify additional references. Information was extracted from eligible articles by the investigators. Study quality was assessed using criteria appropriate for the design of the studies identified to address the three key questions (comparison studies, prognostic studies or cost-effectiveness analyses).

DATA SYNTHESIS

Evidence tables were constructed for each key question to summarize each study included in the review including patient and intervention characteristics, patient outcomes (benefits and harms) and methodological quality. Qualitative syntheses of the available data were done to answer each of the 3 key questions. There were not enough similar studies to pool data using formal meta-analysis in an effort to get more precise estimates. Any findings, or lack thereof, representing the Departments of Veterans Affairs or Defense (DoD) populations were noted.

PEER REVIEW

A draft version of this report was reviewed by the technical expert panel, as well as other expert health care providers. Reviewer comments and our responses are summarized in Appendix C.

RESULTS

The electronic search identified 1,637 citations. Preliminary review of the titles and abstracts excluded 1,491 from further review; 146 were retained for more in-depth review. From these, we identified 3 articles for Key Question #1, 3 articles for Key Question #2 and no articles for Key Question #3. A search of reference lists and identification of recently published studies added one article for each key question.

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?

Conclusion

- A single study provides moderate strength evidence that use of the HeartMate II as a destination left ventricular assist device produces better patient outcomes, including patient survival, with fewer harms and hospitalizations than the HeartMate XVE, the only other ventricular assist device approved by the FDA for destination therapy.

We found one good quality randomized clinical trial of the HeartMate II used as a left ventricular assist device for destination therapy.[1] Patients enrolled in this study met the general criteria for destination therapy that were largely based on enrollment criteria in a previous study of an older generation device[2] including being ineligible for a heart transplant, being symptomatic at rest or with minimal exertion (New York Heart Association [NYHA] class IV heart failure) despite optimization of other therapies for heart failure, and a left ventricular ejection fraction less than 25%. Thus the findings are likely applicable to current candidates for destination therapy. The subjects' (n=200) mean age was 62 years and 84% were male. Compared to the older generation HeartMate XVE left ventricular assist device, use of the HeartMate II had better 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% ($p < 0.0001$). 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 functional 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 than the HeartMate XVE group including major bleeding and strokes.

Currently all cases of destination therapy being registered in a national data base are being treated with the HeartMate II device.[3] Since patient characteristics and outcomes in the HeartMate XVE arm of this randomized comparison of devices were similar to those in the previous clinical trial that demonstrated the HeartMate VE provided superior outcomes compared to optimal medical therapy,[2] one might infer that the HeartMate II would also be superior to optimal medical therapy. Clinical trials of other newer generation continuous flow ventricular assist devices for destination therapy are ongoing, 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?

Conclusion

- The available evidence is insufficient to refine patient or site selection criteria for use of the HeartMate II as destination therapy.

A few studies have identified risk factors for mortality and complications and developed or applied mortality prediction models to this particular patient population. Further studies are needed to validate use of different criteria to 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 device (HeartWare) as destination therapy.[4,5] In the meantime, the approved FDA indication and CMS criteria for coverage are available to guide patient selection.

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?

Conclusion

- A single industry funded analysis has estimated that the cost-effectiveness of using the FDA-approved, current generation LVAD as destination therapy in patients with end-stage heart disease is approximately $200,000 per quality-adjusted life year. The strength of the evidence for this estimate is low.

Even with favorable assumptions regarding the cost and effectiveness of treatment, destination therapy using the current generation, continuous flow ventricular assist device appears to be relatively cost-ineffective compared with traditional standards and other Medicare approved interventions.[6] However, large improvements in cost-effectiveness have occurred in the past decade. If improvements continue to be made, destination therapy in end-stage heart disease with an LVAD may become more cost-effective in the future.

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.
- Develop decision aids to help providers communicate information about the benefits, risks and care needed when patients are considering an approved ventricular assist device as destination therapy and to help providers elicit patients' values and preferences.
- Update cost-effectiveness models as better data become available and incorporate probabilistic sensitivity analyses to assess uncertainty in the cost-effectiveness estimates.
- Conduct a budget impact analysis that specifically addresses the potential impact within the Veterans Health Administration of use of the currently approved continuous flow ventricular assist devices as destination therapy.