Patient-Reported Outcomes in Left Ventricular Assist Device Therapy: A Systematic Review and Recommendations for Clinical Research and Practice
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Patient-Reported Outcomes in Left Ventricular Assist Device Therapy
A Systematic Review and Recommendations for Clinical Research and Practice

Corline Brouwers, MSc; Johan Denollet, PhD; Nicolaas de Jonge, MD, PhD; Kadir Caliskan, MD; Jennifer Kealy; Susanne S. Pedersen, PhD

Background—Technological advancements of left ventricular assist devices (LVAD) have created today’s potential for extending the lives of patients with end-stage heart failure. Few studies have examined the effect of LVAD therapy on patient-reported outcomes (PROs), such as health status, quality of life, and anxiety/depression, despite poor PROs predicting mortality and rehospitalization in patients with heart failure. In this systematic review, we provide an overview of available evidence on the impact of LVAD therapy on PROs and discuss recommendations for clinical research and practice.

Methods and Results—A systematic literature search identified 16 quantitative studies with a sample size \( \geq 10 \) (mean SD age \( 50.1 \pm 12.6 \) years) that examined the impact of LVAD therapy on PROs using a quantitative approach. Initial evidence suggests an improvement in health status, anxiety, and depression in the first few months after LVAD implantation. However, PRO scores of patients receiving LVAD therapy are still lower for physical, social, and emotional functioning compared with transplant recipients. These studies had several methodological shortcomings, including the use of relatively small sample sizes, and only a paucity of studies focused on anxiety and depression.

Conclusions—There is a paucity of studies on the patient perspective of LVAD therapy. To advance the field of LVAD research and to optimize the care of an increasingly growing population of patients receiving LVAD therapy, more well-designed large-scale studies are needed to further elucidate the impact of LVAD therapy on PROs. (Circ Heart Fail. 2011;4:714-723.)

Key Words: left ventricular assist device ■ patient-reported outcomes ■ quality of life ■ review
tile LVAD therapy have a higher rate of complications and are bothered by the clicking noise from the device. In other heart failure populations, psychological morbidity has been associated with poor treatment adherence, poor self-efficacy, and an unhealthy lifestyle. Yet, it is not known whether patients receiving LVAD therapy who have psychological problems are identified and, hence, treated.

In the future, LVAD therapy is likely to be indicated as a bridge to transplantation and as destination therapy worldwide, thereby providing much optimism for the treatment of more heart failure patients in the future. To optimize the management of this growing group of patients, we need to know the impact of LVAD therapy on patients from a patient perspective. Only with such knowledge are we able to improve care after LVAD implantation and to provide patients and families with all the necessary information that they need for effective decision making regarding whether LVAD implantation is aligned with their own preferences and goals.

Hence, the objectives of this systematic review are to provide a detailed overview of available evidence on the impact of LVAD therapy on PROs and suggest recommendations for clinical research and practice.

Methods

Literature Search

The first author (C.B.) performed a literature search on PubMed from January 1980 to May 2011 using a combination of the following search terms: LVAD, left ventricular assist device, anxiety, depression, health status, quality of life, emotional distress, psychological distress, psychological morbidity, and psychosocial. Only full-text empirical studies with a sample size ≥10, examining the impact of LVAD therapy on PROs assessed by standardized clinical interviews or standardized and validated questionnaires, were eligible for inclusion. Articles found by reference searching and articles for which inclusion was questionable were checked by the last author (S.S.P.), after which a consensus was reached between both authors (C.B. and S.S.P.). Of the 250 candidate articles, 26 were identified that matched the inclusion criteria. Sixteen studies 10-14,19-28 emated largely from the same 4 cohorts, as reported in 1 of the other articles. From each cohort, only the most recent article was included (ie, articles with the most optimal study design and largest sample size), except for 2 extra articles that compared 2 groups of patients receiving LVAD therapy with different devices. 12,18,19,25-27 Hence, the current review is based on 16 studies (Figure).

Literature Overview

Detailed information on the 16 studies included in this review are presented in Table 1 and Table 2. The descriptive data detailed later are stratified by studies on pulsatile (Table 1) vs continuous-flow (Table 2) devices. Studies in which patients receiving therapy via both pulsatile and continuous-flow devices were included and were placed in the continuous-flow device table (Table 2).

For the pulsatile devices, the median number of patients included in the 7 studies was 30 (mean ± SD, 36.0 ± 27.2), with the number of patients receiving therapy via LVADs ranging from 10 to 78. The proportion of men ranged from 60% to 99%, and the mean age of study participants was 47.0 ± 13.5 (range, 29–67) years. Three studies 29-31 (42.9%) used a cross-sectional study design, 4 studies 12,26,32,33 (57.1%) used a prospective (comparative) study design, of which 2 (28.6%) were a randomized controlled trial. In most studies, the baseline assessment was conducted before hospital discharge, which varied between 1 and 2 weeks to ~1 month after LVAD implantation. The 3 cross-sectional studies used a variety of assessment times ranging from <6 weeks after implantation to up to 2 months after LVAD implantation. Two studies compared the PROs of LVAD patients with transplant recipients or patients receiving optimal medical treatment. Of all studies, 4 (57.1%) focused on health status, 12,26,32,33 2 (28.6%) on anxiety, 30,32 and 5 (71.4%) on depression; 2 studies focused on both anxiety and depression.

For the continuous-flow devices, the median number of patients included in the 9 studies was 41 (mean ± SD, 201 ± 229.5), with the number of LVAD patients ranging from 17 to 655. The proportion of men ranged from 76% to 100% across studies, and the mean ± SD age of study participants was 51.5 ± 15.7 (range, 46–62.5) years. Two studies (22%) used a cross-sectional study design, 19,34 1 (11%) used a retrospective design, and 6 (66.7%) used a prospective (comparative) study design. The baseline assessment was performed within 1 month after LVAD implantation in the prospective studies. The retrospective study assessed PROs at 12 months after LVAD implantation, and the cross-sectional studies included patients ranging from 2 to 135 months after LVAD implantation. Two studies compared the PROs of LVAD patients with their partners or with transplant recipients. Of all studies, 8 (88.9%) focused on health status, whereas 1 study (11%) focused on depression.

Results

PROs in Studies on Pulsatile Devices

The studies on the first generation of pulsatile LVADs (Thoratec TCI, Heartmate VE/IP [Thoratec Inc, Pleasanton, CA]; Novacor LVAS [WorldHeart Inc, Oakland, CA]; EXCOR [Berlin Heart AG, Berlin, Germany]; or Toyobo LVAD [Toyoobo Ventricular Assist Systems, Toyobo, Osaka Japan]) assessed health status using a prospective design with a
Table 1. Impact of LVAD Therapy on PROs: Pulsatile Devices (7 Studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Subtype of LVAD</th>
<th>No. LVAD</th>
<th>No. Other</th>
<th>Study Design*</th>
<th>Measure</th>
<th>Main Findings</th>
<th>% of Patients With Clinically Meaningful Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dew et al (1999)</td>
<td>Heartmate TCI/Novacor</td>
<td>2/8</td>
<td>55 OMT/97 HTx</td>
<td>P (2 mo)</td>
<td>SIP</td>
<td>Improvement in physical and social functioning (not all domains significant)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rose et al (2001)</td>
<td>Heartmate VE</td>
<td>68</td>
<td>61 OMT</td>
<td>P (RCT) (1 y)</td>
<td>SF-36, MLHFQ‡</td>
<td>Significant improvement in health status</td>
<td>Not reported</td>
</tr>
<tr>
<td>Grady et al (2004)</td>
<td>Heartmate IP/VE</td>
<td>78</td>
<td>...</td>
<td>P (1 y)</td>
<td>QLI, SIP</td>
<td>Total QoL (psychological/health functioning) and functional disability better for HTx vs LVAD, psychological stressors important in LVAD patients. No significant improvement in total QoL scores over time</td>
<td>Not reported</td>
</tr>
<tr>
<td>Laoutaris et al (2010)</td>
<td>EXCOR</td>
<td>15</td>
<td>...</td>
<td>P (RCT) (10 wk)</td>
<td>MLHFQ‡</td>
<td>Training group significantly better health status after 10 wk, no difference in control group</td>
<td>Not reported</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shapiro et al (1997)</td>
<td>Heartmate IP/VE</td>
<td>30</td>
<td>...</td>
<td>C</td>
<td>MMSE</td>
<td>Significant decrease in depression after 1 y</td>
<td>Not reported</td>
</tr>
<tr>
<td>Dew et al (1999)</td>
<td>Heartmate TCI/Novacor</td>
<td>2/8</td>
<td>55 OMT/97 HTx</td>
<td>P (2 mo)</td>
<td>SLC-90</td>
<td>Depressive and anxiety symptoms significantly reduced over time</td>
<td>Not reported</td>
</tr>
<tr>
<td>Dew et al (2000)</td>
<td>Heartmate VE/Novacor</td>
<td>19/18</td>
<td>...</td>
<td>C (1 mo)</td>
<td>SLC-90</td>
<td>Depression and anxiety significantly correlated to LVAD noise, device malfunction, infection, and driveline issues</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rose et al (2001)</td>
<td>Heartmate VE</td>
<td>68</td>
<td>61 OMT</td>
<td>P (1 y)</td>
<td>BDI</td>
<td>Improved depression scores at follow-up, significantly better depression scores vs OMT</td>
<td>Not reported</td>
</tr>
<tr>
<td>Baba et al (2006)</td>
<td>Heartmate VE/Toyobo</td>
<td>13/1</td>
<td>...</td>
<td>C</td>
<td>Diagnostic interview using DSM-IV criteria</td>
<td>50% of patients have ≥ 1 DSM-IV diagnosis</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (4th Edition); HTx, transplant recipients; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MMSE, Mini-Mental State Examination; OMT, optimal medical treatment; QLI, Quality of Life Index; QoL, quality of life; SCL-90, Symptom Checklist-90; SIP, Sickness Impact Profile.

*C, cross-sectional; P, prospective; R, retrospective; RCT, randomized controlled trial.
†Multiple studies on the same study sample.
‡Disease-specific instrument.
Table 2. Impact of LVAD Therapy on PROs: Continuous-Flow Devices (9 Studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Subtype of LVAD</th>
<th>No. LVAD</th>
<th>No. Other</th>
<th>Study Design*</th>
<th>Measure</th>
<th>Main Findings</th>
<th>% of Patients With Clinically Meaningful Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siegenthaler et al (2005)17</td>
<td>Jarvik 2000</td>
<td>17</td>
<td>...</td>
<td>P (3 mo)</td>
<td>MLHQ‡</td>
<td>Health status significantly improved</td>
<td>Not reported</td>
</tr>
<tr>
<td>Slaugther et al (2009)22†</td>
<td>Heartmate VE/Heartmate II</td>
<td>66/134</td>
<td>...</td>
<td>P (2 y)</td>
<td>MLHQ‡, KCCQ (CSS/OSS)‡</td>
<td>Health status improved significantly. No significant difference in health status between pulsatile and continuous devices for MLHQ</td>
<td>Not reported</td>
</tr>
<tr>
<td>Allen et al (2010)35</td>
<td>Heartmate VE/Heartmate II</td>
<td>7/23</td>
<td>...</td>
<td>R</td>
<td>MLHQ‡</td>
<td>Health status scores correlate to NYHA I-II, indicating a relatively low impact of LVAD on health status</td>
<td>Not reported</td>
</tr>
<tr>
<td>Rogers et al (2010)18,22,23,25,27†</td>
<td>Heartmate II 655</td>
<td>...</td>
<td>P (2 y)</td>
<td>MLHQ‡, KCCQ (CSS/OSS)‡</td>
<td>Health status significantly improved</td>
<td>79 BTT, 92 DT patients</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kugler et al (2010)36</td>
<td>Heartmate II 36 54 HTx</td>
<td>...</td>
<td>P (6 mo)</td>
<td>SF-36</td>
<td></td>
<td>No significant improvement in LVAD group over time, HTx group significantly better physical functioning and mental health</td>
<td>Not reported</td>
</tr>
<tr>
<td>Meyer et al (2010)34</td>
<td>Heartmate II/HVAD 17/10</td>
<td>...</td>
<td>C</td>
<td>SF-36</td>
<td></td>
<td>Half of health status domains significantly lower for LVAD vs general population</td>
<td>Not reported</td>
</tr>
<tr>
<td>Bogaev et al (2011)18,22,23,25,27†</td>
<td>Heartmate II 465</td>
<td>...</td>
<td>P (6 mo)</td>
<td>MLHQ‡, KCCQ (CSS/OSS)‡</td>
<td>Health status scores improved significantly. No sex difference in health status scores. Improvements in DT group higher than in BTT</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Starling et al (2011)38</td>
<td>HeartmateVE/Heartmate II/Thoratec pVAD 338</td>
<td>...</td>
<td>P (1 y)</td>
<td>EuroQol EQ-5D</td>
<td>QoL significantly improved at 3–12 mo of LVAD support</td>
<td>Not reported</td>
<td></td>
</tr>
</tbody>
</table>

BTT, bridge-to-transplantation therapy; CSS, Clinical Summary Score; DT, destination therapy; HADS, Hospital Anxiety and Depression Scale; HTx, transplant recipients; IES-R, Impact of Event Scale–Revised; OSS, Overall Summary Score; QoL, quality of life.
*C, cross-sectional; P, prospective; R, retrospective.
†Multiple studies on the same study sample.
‡Disease-specific instrument.
variety of instruments (Table 1). All studies found a significant improvement in the mean health status score (ie, the Minnesota Living with Heart Failure Questionnaire [MLHFQ]) or in at least 2 subdomain scores (ie, the Short-Form Health Survey 36 [SF-36], the Sickness Impact Profile, the LVAD Stressor Scale, and the Quality of Life Index [QoL Index]) at follow-up compared with baseline. The improvement in health status seemed to reach a plateau at ≈3 months after LVAD implantation. The results showed that, during this period, physical disability becomes less prominent and patients feel less fatigued and sleep better, thereby increasing the ability of self-care and ambulation. The impact of the degree of physical disability on health status was also indicated in a recent trial that randomized LVAD patients to an exercise training program versus usual-care. The outcomes demonstrated that improvement in physical exercise capacity in patients in the treatment arm led to a better health status compared with that of the patients in the control arm. Despite improvements in physical functioning, many patients may experience psychosocial problems and impaired psychological well-being, especially at ≈1 month after implantation. The psychological symptoms seem to originate from feelings of sadness, helplessness, irritability, feeling useless to others, and having a sense of loss of control over one’s life; and seem to be associated with worrying about LVAD malfunction, complications, waiting for a donor heart, and being away from family. Depression and anxiety are correlated with LVAD noise, driveline problems, and infection (P<0.05 for all). The prevalence rates of anxiety and depression were lower in LVAD patients than transplant recipients, with transplant recipients experiencing anxiety, depression, and posttraumatic stress disorder. The HeartMate II trial had 2 arms that enabled the investigators to analyze the health status within and between patient groups supported by the HeartMate XVE or the HeartMate II. At the 12-month follow-up, the health status of patients receiving therapy via continuous-flow LVADs was better compared with those receiving therapy via pulsatile devices (MLHFQ, P=0.03; KCCQ-OSS [Overall Summary Score], P=0.06; KCCQ-CSS [Clinical Summary Score], P=0.12), likely caused by the improved durability, decrease in complications, smaller size, and silent operation of the continuous-flow device. Recently, the HeartMate II was also compared with the HeartMate XVE and the Thoratec pVAD in a commercial setting to investigate the relative efficacy and risk profile, in patients enrolled in the Interagency Registry for Mechanically Assisted Circulatory Support. Health status appeared to improve equally for the 2 groups of devices (P<0.001) after 3 months to 1 year. Patients receiving therapy via pulsatile and continuous-flow devices were not significantly different on symptoms of anxiety, depression, and posttraumatic stress disorder. The cross-sectional study of Meyer et al found no significant differences in domain scores between 2 continuous-flow systems: the centrifugal-flow pump Heartmate II and the axial-flow pump HVAD. From both arms of the HeartMate II trial, patients were also selected based on their device indication (ie, bridge-to-transplant or destination therapy) and compared on paired health status scores. The group of LVAD patients indicated for destination therapy had a higher improvement in median health status scores between baseline and 6 months than the group of LVAD patients indicated for bridge-to-transplant therapy (MLHFQ, -40 vs -29 points; KCCQ-OSS, 39 vs 28 points; KCCQ-CSS, 36 vs 24 points, respectively). In this study, 79% of the bridge-to-transplant patients and 92% of the destination therapy patients with paired data had achieved a clinically meaningful improvement of ≥5 points in their KCCQ-OSS and KCCQ-CSS scores compared with baseline. Compared with transplant recipients and healthy controls, LVAD patients reported considerably poorer health status at

PROs in Studies on Continuous-Flow Devices
The most intensively studied continuous-flow device used in the studies included for the review was the HeartMate II (Thoratec Inc). Other devices included the Micromed DeBakey (Micromed Cardiovascular Inc, Houston, TX), INCORE (Berlin Heart AG), Jarvik 2000 (Jarvik Heart, Inc, New York, NY), or HVAD device (HeartWare Inc, Framingham, MA) (Table 2). Almost all studies on patients with a continuous-flow LVAD show significant improvements in mean health status scores, using the MLHFQ, Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-36, and EuroQol EQ-5D (EQ-5D), from baseline up to the 3-, 6-, and 12-month follow-up (P<0.05 for all),18,25,27,34,35,37,38 Only the study by Kugler et al found no significant improvement in health status using the SF-36 at the 6-month follow-up. Whether this was due to psychosocial problems or a lower physical exercise tolerance is not clear, because both may ultimately restrict patients’ opportunities to re-engage in professional and recreational activities, which are known predictors for long-term health status. In recent years, several articles have been published on comparative studies between LVAD patients with different devices and in different clinical settings or between LVAD patients and transplant recipients and healthy controls. The HeartMate II trial had 2 arms that enabled the investigators to analyze the health status within and between patient groups supported by the HeartMate XVE or the HeartMate II. At the 12-month follow-up, the health status of patients receiving therapy via continuous-flow LVADs was better compared with those receiving therapy via pulsatile devices (MLHFQ, P=0.03; KCCQ-OSS [Overall Summary Score], P=0.06; KCCQ-CSS [Clinical Summary Score], P=0.12), likely caused by the improved durability, decrease in complications, smaller size, and silent operation of the continuous-flow device.
baseline \( (P=0.0032) \) and at the 6-month follow-up \( (P=0.016) \), especially with respect to mental health and physical functioning\(^{34,36} \) and with respect to the social functioning, role physical functioning, and role emotional functioning domains of the SF-36.\(^{34} \)

Overall, evidence on the impact of the duration of living with an LVAD, the initial diagnosis, and sex and age disparities in health status is scarce among LVAD patients. Women tend to have been underrepresented in LVAD studies, with one study finding no significant sex differences among LVAD patients \( (MLHFQ, \ P=0.661; \ KCCQ-OSS, \ P=0.706; \ KCCQ-CSS, \ P=0.371) \).\(^{18} \)

### Discussion

#### Summary of the Findings

This review indicates that LVAD patients experience an improvement in health status, particularly in the first 3 months after LVAD implantation and discharge. This trend was visible irrespective of the type of device (pulsatile vs continuous-flow devices) and clinical setting (destination and bridge-to-transplant therapy). Results also indicated that LVAD patients supported by continuous-flow devices and destination therapy show the greatest improvements in health status after implantation.

Few studies have examined the prevalence of anxiety and depression in LVAD patients, in particular in patients receiving therapy via continuous-flow LVADs. Patients supported by pulsatile devices showed relatively high mean depression scores just after LVAD implantation.\(^{26,29,31} \) The retrospective study\(^{19} \) of Bunzel et al\(^{20} \) found no significant difference in depression scores between patients receiving therapy via pulsatile vs continuous-flow devices; these patients might be more vulnerable to psychological distress, based on the higher rate of complications and the characteristics of the device (eg, short durability, large size, noise, and large batteries). Hence, these differences in findings could well be explained by sample size limitations, differences in subtype of devices, and the time of collecting data.

The LVAD patients report better health status and fewer symptoms of anxiety and depression when compared with their partners and with patients receiving optimal medical treatment, but not when compared with transplant recipients. In contrast to transplant recipients, LVAD patients are recurrently reminded of their device because of the need to clean the driveline insertion site and change batteries frequently.\(^{15} \)

Furthermore, organ recipients appear to redefine “normal” life and what it entails after transplantation.\(^{32} \)

Overall, there was a substantial difference between the studies in the handling and reporting of PROs, depending on whether PROs were assessed as primary or secondary outcomes. In Table 3, the details on the number of patients alive from baseline to end of follow-up, the estimated percentage of those patients having PRO data, and the cause of missing data were outlined for all prospective studies assessing health status in LVAD patients. Except for the Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure trial,\(^{26} \) all studies on pulsatile devices assessed health status as a primary outcome, whereas this only holds true for 1 continuous-flow study.\(^{36} \) The percentage of PRO data obtained from the patients alive over time was 92% to 100% in the pulsatile device studies and 46% to 91% in the continuous-flow device studies. At the end of the full study, this percentage was unchanged for the pulsatile device studies and was 49% to 89% for the continuous-flow device studies. In 2 continuous-flow device studies, the follow-up period for the PROs was shorter than the follow-up period for the full study, causing an absence of PRO data at the final time points.\(^{18,25} \) For those studies, the percentage of PRO data obtained was calculated based on the number of patients alive at the end of the PRO follow-up period rather than at the end of the full study. Most studies indicated similar reasons for the missing data (eg, patient exclusion, deceased, too ill, heart transplantation, or dropout). None of the studies reported cognitive limitations or psychological distress as a reason for missing data.

#### Limitations of the Review

Because of the different time era of the studies included in this review and the heterogeneity of the studies (differences in follow-up assessments, sample sizes, and PRO assessment), it was not possible to perform a formal meta-analysis. Although increasing the statistical power of the findings by excluding studies with a small sample size \( (N<10) \), this resulted in fewer articles eligible for inclusion. In turn, this could have potentially created a bias toward results found in larger studies. The proportion of female patients across studies was relatively low; hence, it is not feasible to generalize the findings to women with an LVAD. There was a considerable difference in the percentage of missing PRO data between the pulsatile and continuous-flow device studies. This is most probably caused by the fact that most of the pulsatile device studies assessed PROs as primary outcomes but was also because of shorter follow-up times, thereby decreasing the chance of death, heart transplantation, and drop out. Only 3 studies\(^{18,36,37} \) reported how they dealt with loss of data, which included comparing the baseline characteristics of patients for whom data were and were not available or substituting the missing scores by the maximum negative score of the used instrument. Correcting for missing data did not affect the outcomes in these studies. Other studies calculated the percentage and significance of improvement by simply comparing the group total scores of patients with paired data between baseline and follow-up. However, the number of patients with paired data decreases significantly over time, which may increase the probability of finding a significant improvement because the sicker patients are usually lost to follow-up. More information is needed on intraindividual changes and the proportion of patients who experience a clinically relevant change.

Moreover, the instruments chosen for the study might not have been sufficiently sensitive to tap LVAD-related changes in health status, if present.\(^{36} \) Some instruments, such as the KCCQ, have also not been used optimally, because authors did not report subdomain scores. Finally, studies failed to examine key predictors of intraindividual changes in PROs over time or associations between PROs and other outcomes, such as mortality and number of hospitalizations.
Table 3. Overview of Sample Size, Follow-Up, and Missing Data of LVAD Studies With Health Status Assessments

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Other</th>
<th>Maximum Follow-Up Reported*</th>
<th>Baseline 2 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>1 y</th>
<th>2 y</th>
<th>Mean % of Living Patients With PRO Data Overall</th>
<th>% of Living Patients With PRO Data at the End of Follow-Up</th>
<th>Reason for Missing Data at Inclusion and Follow-Up</th>
<th>Information on Handling of Missing Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulsatile devices</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Dew et al (1999)</td>
<td>55 OMT/97 HTx</td>
<td>P (2 mo)</td>
<td>10</td>
<td>10</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>All patients</td>
<td>All patients</td>
<td>HTx, too ill, refused, or language issue</td>
<td>No</td>
</tr>
<tr>
<td>Rose et al (2001)</td>
<td>61 OMT</td>
<td>P (RCT)</td>
<td>68</td>
<td>...</td>
<td>...</td>
<td>38</td>
<td>24</td>
<td>5</td>
<td>92.0</td>
<td>Deceased, too ill, or no transportation</td>
<td>No</td>
</tr>
<tr>
<td>Grady et al (2004)</td>
<td>...</td>
<td>P (1 y)</td>
<td>78</td>
<td>...</td>
<td>...</td>
<td>43</td>
<td>9</td>
<td>All patients</td>
<td>All patients</td>
<td>HTx, too ill, refused, or deceased</td>
<td>No</td>
</tr>
<tr>
<td>Laoutaris et al (2010)</td>
<td>...</td>
<td>P (RCT) (10 wk)</td>
<td>15</td>
<td>15</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>All patients</td>
<td>All patients</td>
<td>...</td>
<td>No</td>
</tr>
<tr>
<td><strong>Continuous-flow devices</strong></td>
<td></td>
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<tr>
<td>Siegenthaler et al (2005)</td>
<td>...</td>
<td>P (3 mo)</td>
<td>17</td>
<td>...</td>
<td>...</td>
<td>11</td>
<td>7</td>
<td>4</td>
<td>61.3</td>
<td>Deceased</td>
<td>No</td>
</tr>
<tr>
<td>Slaugther et al (2009)</td>
<td>...</td>
<td>P (2 y)</td>
<td>200</td>
<td>...</td>
<td>...</td>
<td>127</td>
<td>101</td>
<td>64</td>
<td>77.6</td>
<td>Deceased, HTx</td>
<td>No</td>
</tr>
<tr>
<td>Rogers et al (2010)</td>
<td>...</td>
<td>P (2 y)</td>
<td>655</td>
<td>...</td>
<td>460</td>
<td>380</td>
<td>213 (only DT)</td>
<td>101 (only DT)</td>
<td>82.5 BTT, 90.7 DT</td>
<td>82.8 BTT, 88.5 DT</td>
<td>Deceased, HTx, staff availability, scheduling</td>
</tr>
<tr>
<td>Kugler et al. (2010)</td>
<td>54 HTx</td>
<td>P (6 mo)</td>
<td>36</td>
<td>...</td>
<td>...</td>
<td>34</td>
<td>...</td>
<td>...</td>
<td>75.0</td>
<td>Deceased, refused, or dropped out</td>
<td>Yes</td>
</tr>
<tr>
<td>Bogaev et al (2011)</td>
<td>...</td>
<td>P (6 mo)</td>
<td>465</td>
<td>...</td>
<td>...</td>
<td>251</td>
<td>150</td>
<td>121 (18 mo)</td>
<td>79.5</td>
<td>Deceased, HTx, staff availability</td>
<td>Yes</td>
</tr>
<tr>
<td>Starling et al (2011)</td>
<td>...</td>
<td>P (1 y)</td>
<td>338</td>
<td>...</td>
<td>306</td>
<td>196</td>
<td>128</td>
<td>...</td>
<td>46.1</td>
<td>Not reported</td>
<td>No</td>
</tr>
</tbody>
</table>

BTT, bridge-to-transplantation therapy; DT, destination therapy; HTx, heart transplantation; OMT, optimal medical treatment.
*C, cross-sectional; P, prospective; R, retrospective; RCT, randomized controlled trial.
†Multiple studies on the same study sample.
Table 4. Recommendations for the Incorporation of PRO Assessments in Clinical Practice and Future Research

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical Practice</th>
<th>Future Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpose of incorporating PROs in clinical practice and research</td>
<td>PROs have unique prognostic value beyond physician-rated measures and information derived from patients’ medical status</td>
<td>Evaluate the impact of treatment, devices, and device settings on PROs using both health status and anxiety/depression measures</td>
</tr>
<tr>
<td></td>
<td>Inclusion of the patient perspective; no proxy measure available from measures assessed in a standard clinical setting</td>
<td>Comparison of PROs between LVAD patients and other groups (eg, patients receiving optimal medical treatment, HTx) is necessary for informed political and clinical decision making</td>
</tr>
<tr>
<td></td>
<td>PROs may facilitate communication between patients and physicians</td>
<td>Compare the sensitivity of disease-specific and generic PRO measures to detect changes over time; if necessary, develop new disease-specific measures (eg, to assess anxiety and depression)</td>
</tr>
<tr>
<td></td>
<td>PROs may enhance identification of high-risk patients whose medical treatment needs to be optimized</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PROs can be used as performance measures to evaluate the quality of care</td>
<td></td>
</tr>
<tr>
<td>Recommendations for PROs as primary outcomes in LVAD research and therapy</td>
<td>Enables more accurate tracking of changes in patient’s physical and psychological functioning over time and better coordination of care (eg, individually tailored rehabilitation programs)</td>
<td>Examine the correlation between clinical variables and PROs and determine their relative importance for LVAD patient prognosis</td>
</tr>
<tr>
<td></td>
<td>A no-risk, low-cost, and low-burden addition to clinical care</td>
<td>Use both an interindividual and intrapatient approach in data analyses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adhere to CONSORT and STROBE statement guidelines for reporting critical PRO data elements (eg, missing data and clinically meaningful improvement)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of disease-specific questionnaires (eg, MLHFQ, KCCQ) in studies with LVAD cohorts only</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Incorporate PRO instruments for anxiety and depression in studies on continuous-flow devices</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use prospective studies with large sample sizes</td>
</tr>
</tbody>
</table>

CONSORT, Consolidated Standards of Reporting Trials; MLHFQ, Minnesota Living with Heart Failure Questionnaire; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Need for Assessing PROs in LVAD Patients

The importance of studying PROs, such as health status, is gaining increased recognition because of the belief that an illness, its treatment, and complications affect all domains of a patient’s life and that the patient perspective is as valid as that of the clinician when evaluating outcomes. In addition, information on PROs is important for future patients and families who have to make an informed decision regarding the option for LVAD therapy. Information on PROs cannot be extracted from patients’ medical records or a proxy and, therefore, PROs need to be assessed in their own right. Thus, PROs may provide important additional information to health care providers and serve as targets for intervention in individual patients.

Despite their importance, there is often a minor emphasis placed on PROs, and they are rarely included as primary outcomes in clinical LVAD trials. In particular, studies on continuous-flow LVADs show a tendency to neglect anxiety and depression. This is surprising given that 15% to 36% of patients with heart failure experience depression,40,41 40% experience anxiety,16 and 10% to 17% experience posttraumatic stress disorder.42,43 Symptoms of depression and anxiety can be disabling15 and are associated with an increased risk of declines in physical health,16 mortality, higher medication costs,15 noncompliance with treatment, malignancies,44,45 and hospital readmissions.8 The limited available evidence suggests that there may be a link between LVAD technology and the patient’s psychological adjustment.5

Recommendations for Future Research and Care of LVAD Patients

Because it has been widely established that LVAD therapy is capable of enhancing the survival of patients with end-stage heart failure, measuring PROs (eg, functional status, quality of life, and psychological distress) in these patients deserves a priority similar to survival in future LVAD studies. This review indicates that PROs improve over time, yet it also uncovers major shortcomings in their assessment, reflecting a considerable knowledge gap in the optimal care for these patients. More specific recommendations for future research and clinical practice in LVAD therapy are given in Table 4.

In addition to the current interindividual approach (comparing changes in mean group scores over time), PROs should also be analyzed using an intrapatient approach focusing on the proportion of patients who experience a clinical improvement or deterioration over time. Eventually, this will create the possibility of risk stratifying patients and enhancing optimal clinical practice.

Appropriate care should also be given when selecting PRO measures, with a distinct preference for disease-specific measures, such as the KCCQ or MLHFQ. Patients are more likely to...
identify themselves in these instruments, thereby increasing the response rate. In studies on continuous-flow devices, health status was predominantly measured with the KCCQ or the MLHFQ, with both measures showing similar results in various large-scale LVAD studies.\textsuperscript{18,22,23,25,27} This suggests that these measures are sensitive for detecting LVAD-related changes in health status over time, if present. To capture psychological morbidity in LVAD patients, the Heart Failure Symptom Checklist or LVAD Stressor Scale could be used in addition to specific anxiety/depression measures. Given the paucity of studies on psychological functioning in LVAD patients, it is difficult to recommend a specific instrument to use. The Patient Health Questionnaire [PHQ-9] and the Generalized Anxiety Disorder [GAD-7] Scale might be a way to start, because both instruments have excellent psychometric properties. In addition, these measures are exempt from copyright and can be used free of charge.

It is paramount that future studies comply with the Consolidated Standards of Reporting Trials [CONSORT] and the Strengthening the Reporting of Observational studies in Epidemiology [STROBE] guidelines for reporting randomized trials and observational studies.\textsuperscript{46,47} These guidelines also stipulate reporting of missing data and clinical relevance, as has also been advocated by others.\textsuperscript{48,49} This is needed because, for sufficiently large trials, it is possible to have a statistically significant difference that may not be clinically meaningful.\textsuperscript{49} In clinical practice, there needs to be a shift in LVAD rehabilitation programs from survival to also focus on coping abilities and health status of LVAD patients. These programs need to be tailored to the individual patient and should also account for the patient’s level of emotional functioning.

Conclusion
There is a paucity of studies on the patient perspective of LVAD therapy. Initial evidence suggests an improvement in health status, anxiety, and depression in the first months after LVAD implantation. However, PRO scores of LVAD patients are still lower for physical, social, and emotional functioning compared with transplant recipients. To advance the field of LVAD research and to optimize the management of an increasingly growing population of LVAD patients, more well-designed large-scale studies on PROs are needed. By these studies, we will be able to further elucidate the psychological and social impact of LVAD therapy, thereby creating the opportunity to improve the care for patients after LVAD implantation and to provide important information that is needed by patients and families for effective decision making regarding whether LVAD implantation is aligned with their own preferences and goals.

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This research was in part supported with a VIDI grant (91710393) from the Netherlands Organization for Health Research and Development, The Hague, The Netherlands (Dr Pedersen).

Disclosures
None.

References


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Brouwers et al.

Patient-Reported Outcomes in LVAD Therapy


**CLINICAL PERSPECTIVE**

Evidence suggests that patients receiving left ventricular assist device (LVAD) therapy experience an improvement in health status over time, independent of device type and setting. However, although their physical disability becomes less prominent after implantation, many patients experience difficulties with psychological adjustment, especially early after implantation, which is associated with worrying about LVAD malfunction, complications, waiting for a donor heart, and being away from family. Furthermore, overall functioning of LVAD patients is still more impaired compared with transplant recipients on physical, social, and emotional functioning. Extensive information on patient-reported outcomes in LVAD patients is limited, with many of the existing studies having methodological shortcomings. To advance the field of LVAD research and to optimize the care of an increasingly growing population of LVAD patients, more well-designed large-scale studies are needed to further elucidate the impact of LVAD therapy on patient-reported outcomes.