Published in final edited form as:

ASAIO J. 2021 October 01; 67(10): 1159–1162. doi:10.1097/MAT.0000000000001378.

The Impact of Adverse Events on Functional Capacity and Quality of Life after HeartWare Ventricular Assist Device Implantation

Marc D Samsky, MD[1], **Carmelo Milano, MD**[1], **Salpy Pamboukian, MD, MSPH**[2], **Mark S Slaughter, MD**[3], **Emma Birks, MD, PhD**[3], **Steven Boyce, MD**[4], **Samer Najjar, MD**[5], **Akinobu Itoh, MD**[6], **Bruce Reid, MD**[7], **Nahush Mokadam, MD**[8], **Keith D Aaronson, MD**[9], **Francis Pagani, MD**[9], **Joseph G Rogers, MD**[1]

[1]Duke University Medical Center, Durham, NC

[2]University of Alabama at Birmingham, Birmingham, AL

[3]University of Louisville, Louisville, KY

[4]Washington Hospital Center, Washington DC

[5]MedStar Washington Hospital Center, Washington, DC

[6]Washington University, St Louis, MO

[7]Intermountain Medical Center, Murray, UT

[8]University of Washington, Seattle, WA

[9]University of Michigan, Ann Arbor, MI

Abstract

LVADs improve quality of life (QoL) and functional capacity (FC) for patients with advanced heart failure. The association between adverse events (AEs) and changes in QoL and FC are unknown.

Patients treated with the HeartWare™ HVAD™ with paired six-minute walk distance (6MWD, n=263) and Kansas City Cardiomyopathy Questionnaires (KCCQ, n=272) at baseline and 24 months in the ENDURANCE and ENDURANCE Supplemental Trial databases were included. Patients were stratified based upon occurrence of clinically significant AEs during the first 24 months of support and analyzed for the mean change in 6MWD and KCCQ. The impact of AE frequency on change in 6MWD and KCCQ from baseline to 24 months was evaluated.

Of the AEs examined, only sepsis was associated with an improvement in 6MWD (109m vs. 16m, p=0.002). Patients without improvement in 6MWD test from baseline to 24 months had significantly more AEs than those with FC improvement (p=0.0002). AEs did not affect the KCCQ overall summary score.

Corresponding Author Joseph G. Rogers, MD, Professor of Medicine, Cardiology, Duke University School of Medicine, Box 3034 DUMC, Durham, NC 27710, Joseph.rogers@duke.edu.

In this analysis, patients with fewer AEs had greater improvement in FC during the 24 month follow up. The frequency of AEs did not have a significant impact on quality of life after LVAD implantation.

Keywords

Left ventricular assist device; adverse events; patient centered outcomes

INTRODUCTION

Advanced heart failure (HF) is characterized by profound functional limitation, decreased quality of life (QoL) and high mortality rates.[1] Cardiac transplantation remains the therapeutic gold standard for patients with HF refractory to medical therapy, but the shortage of suitable donor organs limits the potential benefit to a small and select cohort.[2, 3] The use of durable mechanical circulatory support devices has been established as an alternative, permanent therapy for patients with end-stage HF ineligible for cardiac transplantation.[3–6] Studies have demonstrated improved functional capacity and QoL following durable left ventricular assist device (LVAD) implantation, despite the occurrence of adverse events (AEs).[7, 8] However, the impact of adverse events on functional capacity and QoL is not well-characterized. We therefore sought to determine the impact of AEs on these measures in the two years following LVAD implantation in patients ineligible for cardiac transplantation.

METHODS

Data from patients implanted with a HeartWare™ HVAD™ System enrolled in the ENDURANCE[9] and ENDURANCE Supplemental randomized trials[8] (n=604) was used for this analysis. In both trials, the 6-minute walk distance (6MWD) was used to assess sub-maximal functional capacity and the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score was used to assess QoL. Twelve AEs were examined and were included if they occurred at any time within the 24-month follow up period. The AEs included gastrointestinal bleeding (GIB), major infection, sepsis, driveline infection, respiratory failure, renal dysfunction, overall neurological dysfunction, hemorrhagic cerebrovascular accident (HCVA), ischemic cerebrovascular accident (ICVA), right heart failure (RHF), device malfunction/failure, and pump thrombosis. Definitions for each AE are listed in the Appendix.

Study Subjects.

Patients with paired 6MWD at baseline and 24 months (n=263), and paired KCCQ measurement at baseline and 24 months (n=272) were included. Separate analyses were conducted for 6MWD and KCCQ; patients with complete follow up data for each assessment were included in both analysis cohorts. Patients were sub-stratified based on the occurrence of each AE to determine impact on 6MWD and KCCQ.

Temporal changes in 6MWD and KCCQ were analyzed based upon the cumulative burden of the 12 AEs of interest by summing the total number of adverse events during the

24-month follow up. 6MWD change from baseline to 24 months was grouped as follows: ≤ 0 meter (n=98), 1–199 meters (n=95), and ≥ 200 meters (n=70). KCCQ change from baseline to 24 months was grouped as follows: ≤ 20 points (n=103), 20–40 points (n=80), and ≥ 40 points (n=89).

Means are presented with standard deviations, continuous 6MWD and QoL metrics were compared using a t-test for those with and without AEs. Analysis of variance (ANOVA) was used when comparing the cumulative burden of AEs for the QoL and KCCQ groupings. If the overall model p-value was below 0.05, Tukey's Studentized Range multiple comparison test was used to identify pairwise differences. A Bonferroni adjustment was made for multiple testing by dividing 0.05 by the number of tests simultaneously taking place. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Inc. Cary, NC).

RESULTS

Demographics and baseline clinical characteristics of patients included in this analysis are shown in Table 1. The mean age of the overall cohort was 63.6 ± 11.5 years, 79.1%% were male, 74.3%% were white, and the mean BMI was 27.7 ± 5.9 kg/m^2. Most patients had an ischemic cardiomyopathy (56.6%), were being treated with medications for hypertension (70.4%), and nearly half had diabetes. Overall, 76.2% of patients were INTERMACS profile 1–3 and 17.4% had a prior stroke. Baseline measurements of functional capacity and quality of life demonstrated a marked reduction in both submaximal exercise performance with a mean 6MWD of 106.4 ± 131.1 meters and baseline quality of life as measured by the KCCQ overall summary score with a mean overall summary score of 38.9 ± 20.8.

Functional Capacity.

Paired assessments of 6MWD were available in 263 patients. Patients with greater improvements in 6MWD were significantly younger than those with less improvement (Table 1) and had fewer major AEs during the 24-month follow up. Patients experiencing a greater number of cumulative AEs had less improvement in 6MWD than those with fewer events (p=0.008; Table 2). While patients who experienced an AE had less improvement in 6MWD overall relative to those who did not, only an episode of sepsis during the follow-up period was associated with less improvement in 6MWD distance, which remained significant following adjustment for multiple testing (109 vs 16 meters, p=0.002; Figure 1).

Quality of Life.

Paired assessments of KCCQ were available in 272 patients. There were no significant differences in baseline characteristics among patients with the greatest improvements in KCCQ scores compared to those with less improvement. Improvement in KCCQ during the follow-up period did not differ significantly among the groups, although patients with greater improvement tended to have fewer major AEs (p=0.10). (Table 2). Figure 2 shows mean KCCQ score change from baseline through 24-months stratified by specific major AE. Mean KCCQ score changes were not statistically different among the major AEs.

DISCUSSION

This analysis demonstrates that in a contemporary cohort of patients with end-stage HF ineligible for cardiac transplantation, less frequent AEs were associated with greater improvement in submaximal exercise performance. Interestingly, long-term QoL improvements were not statistically linked to AEs. Although AEs were directionally associated with reduced 6MWD, only sepsis was associated with a statistically significant reduction in functional capacity. There were no associations between AE type and significant reduction in QoL.

The current report is the first and largest to define the impact of AEs on functional capacity and QoL in patients implanted with a centrifugal-flow LVAD who were otherwise ineligible to undergo cardiac transplantation. Previous studies have included legacy LVAD devices or second generation axial flow devices in cohorts of patients potentially awaiting heart transplantation.[10, 11]

As part of the ENDURANCE Trial, patients randomized to receive the HVAD System experienced significantly higher rates of stroke, right heart failure, and sepsis compared to the control device. The increased rate of strokes associated with HVAD therapy occurred primarily within the first 6 months following implantation, and was associated with mean arterial blood pressures above 90 mmHg.[12] As part of the follow up ENDURANCE Supplemental Trial, patients randomized to the HVAD System were required to follow blood pressure management protocols, and this resulted in an overall reduction in the incidence of neurological events, especially hemorrhagic strokes, compared to the ENDURANCE Trial.[13] Despite the occurrence of stroke events, there were substantial and significant improvements in functional status and QoL in patients randomized to HVAD therapy observed in both trials.[12, 13] The current analysis from a larger dataset confirms that survivors of ischemic stroke, hemorrhagic stroke, or neurological injury had no differences in degree of improvement in functional status or HF-related QoL at 24-months post-HVAD implantation.

Patients in the ENDURANCE and ENDURANCE Supplemental Trials had markedly abnormal pre-implant functional capacity and QoL despite optimal medical and electro-mechanical therapies for HF, highlighting the associated morbidity and lack of effective treatment options for patients with Stage D HF.[12, 13] In totality, the results of this analysis combined with data from the ENDURANCE and Supplemental Trials, support use of the HVAD as an effective long-term therapy to improve functional capacity and QoL in patients with end-stage HF who are otherwise not candidates for heart transplantation.

In a contemporary cohort of patients recruited from a nationally representative sample, HF patients identified independently performing self-care, regaining mobility, reducing HF symptoms and reducing mortality are important considerations when choosing therapies for HF.[14] The results of this analysis demonstrate that despite frequent AEs, patients with refractory end-stage HF derive significant improvement from HVAD therapy in desired outcomes including functional status and HF-related QoL. Furthermore, AEs that clinicians

often consider to be the most serious (i.e. stroke or neurological impairment) have little impact on the magnitude of improvement in functional capacity or HF-related QoL.

LIMITATIONS

This analysis does not have serial measures of functional capacity and QoL, nor when AEs occurred relative to implant or outcome assessment. Therefore, it is difficult to assess the temporal relationships of the AE to outcomes. We did not measure concomitant use of HF medical therapies which may have also affected functional capacity and HF-related QoL. This analysis was limited to patients who survived for 24-months with completed follow up assessments, and therefore there is potential for survivor bias in that patients with more severe AEs did not survive or patients with more severe AEs did not complete follow up assessment. This may have attenuated the relationship between AE and change in functional capacity or quality of life. Finally, we did not quantify stroke severity; however, data from the ENDURANCE and ENDURANCE Supplemental Trials showed that in follow-up, a substantial number of patients had a modified Rankin score of ≤ 3, suggesting at most moderate residual disability.[12, 13]

CONCLUSIONS

In a contemporary cohort of patients with end-stage HF refractory to optimal medical therapy and who are ineligible to undergo cardiac transplantation, long-term HVAD therapy improves functional capacity and QoL despite frequent AEs. Furthermore, the type of AE had little effect on degree of improvement in functional capacity and QoL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Funding: The ENDURANCE clinical trial program was sponsored by HeartWare (now Medtronic). Statistical support for this manuscript was provided by Medtronic. The authors had access to all the data and are responsible for critical review, writing, and content control.

Conflict of Interest: Marc Samsky: salary supported by NIH T32 training grant (HL069749), Carmelo Milano: None, Salpy Pamboukian: None, Mark Slaughter: Research grant funding from Heartware/Medtronic, Emma Birks: None, Steven Boyce: None, Samer Najjar: None, Akinobu Itoh: None, Bruce Reid: None, Nahush Mokadam: Consultant Abbott, Medtronic, SynCardia, Carmat, Keith Aaronson: None, Francis Pagani: None, Joe Rogers: None

ABBREVIATIONS

HF	Heart failure
QoL	Quality of life
LVAD	Left ventricular assist device
AE	adverse events
KCCQ	Kansas City Cardiomyopathy Questionnaire

6MWD	6-minute walk distance
GIB	Gastrointestinal bleeding
HCVA	Hemorrhagic cerebrovascular accident
ICVA	Ischemic cerebrovascular accident
RHF	Right heart failure

REFERENCES

1. Benjamin EJ, Muntner P and Bittencourt MS. Heart disease and stroke statistics-2019 update: A report from the American Heart Association. Circulation. 2019;139:e56-e528.
2. Samsky MD, Patel CB, Owen A, Schulte PJ, Jentzer J, Rosenberg PB, Felker GM, Milano CA, Hernandez AF and Rogers JG. Ten-year experience with extended criteria cardiac transplantation. Circulation Heart failure. 2013;6:1230–8. [PubMed: 24088293]
3. Daneshmand MA, Krishnamoorthy A, Samsky MD, Felker GM, Pura JA, Lokhnygina Y, Hernandez AF, Rosenberg PB, Blue LJ, Schroder JN, Rogers JG, Milano CA and Patel CB. Comparison of 2-Year Outcomes of Extended Criteria Cardiac Transplantation Versus Destination Left Ventricular Assist Device Therapy Using Continuous Flow. The American journal of cardiology. 2015;116:573–9. [PubMed: 26092273]
4. Jorde UP, Kushwaha SS, Tatooles AJ, Naka Y, Bhat G, Long JW, Horstmanshof DA, Kormos RL, Teuteberg JJ, Slaughter MS, Birks EJ, Farrar DJ and Park SJ. Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular assist device: a prospective study using the INTERMACS registry (Interagency Registry for Mechanically Assisted Circulatory Support). Journal of the American College of Cardiology. 2014;63:1751–7. [PubMed: 24613333]
5. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM 3rd, Long JW, Wozniak TC, Ghumman W, Farrar DJand Frazier OHAdvanced heart failure treated with continuous-flow left ventricular assist device. The New England journal of medicine. 2009;361:2241–51. [PubMed: 19920051]
6. Park SJ, Milano CA, Tatooles AJ, Rogers JG, Adamson RM, Steidley DE, Ewald GA, Sundareswaran KS, Farrar DJ and Slaughter MS. Outcomes in advanced heart failure patients with left ventricular assist devices for destination therapy. Circulation Heart failure. 2012;5:241–8. [PubMed: 22282104]
7. Allen JG, Weiss ES, Schaffer JM, Patel ND, Ullrich SL, Russell SD, Shah AS and Conte JV. Quality of life and functional status in patients surviving 12 months after left ventricular assist device implantation. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2010;29:278–85.
8. Milano CA, Rogers JG, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Mokadam NA, Mahr C, Miller JS, Markham DW, Jeevanandam V, Uriel N, Aaronson KD, Vassiliades TA and Pagani FD. HVAD: The ENDURANCE Supplemental Trial. JACC Heart failure. 2018;6:792–802. [PubMed: 30007559]
9. Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Boyce SW, Najjar SS, Jeevanandam V, Anderson AS, Gregoric ID, Mallidi H, Leadley K, Aaronson KD, Frazier OH and Milano CA. Intrapericardial Left Ventricular Assist Device for Advanced Heart Failure. The New England journal of medicine. 2017;376:451–460. [PubMed: 28146651]
10. Rogers JG, Aaronson KD, Boyle AJ, Russell SD, Milano CA, Pagani FD, Edwards BS, Park S, John R, Conte JV, Farrar DJ and Slaughter MS. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. Journal of the American College of Cardiology. 2010;55:1826–34. [PubMed: 20413033]
11. de Jonge N, Kirkels H, Lahpor JR, Klopping C, Hulzebos EJ, de la Riviere AB and Robles de Medina EO. Exercise performance in patients with end-stage heart failure after implantation of a

left ventricular assist device and after heart transplantation: an outlook for permanent assisting? Journal of the American College of Cardiology. 2001;37:1794–9. [PubMed: 11401113]

12. Rogers JG, Pagani FD, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Boyce SW, Najjar SS, Jeevanandam V and Anderson AS. Intrapericardial left ventricular assist device for advanced heart failure. New England Journal of Medicine. 2017;376:451–460.
13. Milano CA, Rogers JG, Tatooles AJ, Bhat G, Slaughter MS, Birks EJ, Mokadam NA, Mahr C, Miller JS and Markham DW. HVAD: the ENDURANCE supplemental trial. JACC: Heart Failure. 2018;6:792–802. [PubMed: 30007559]
14. Samsky MD, Lin L, Greene SJ, Lippman SJ, Peterson PN, Heidenreich PA, Laskey WK, Yancy CW, Greiner MA, Hardy NC, Kavati A, Park S, Mentz RJ, Fonarow GC, O'Brien EC. Patient Perceptions and Familiarity With Medical Therapy for Heart Failure. JAMA Cardiology. 2020;5(3):292–299 [PubMed: 31734700]

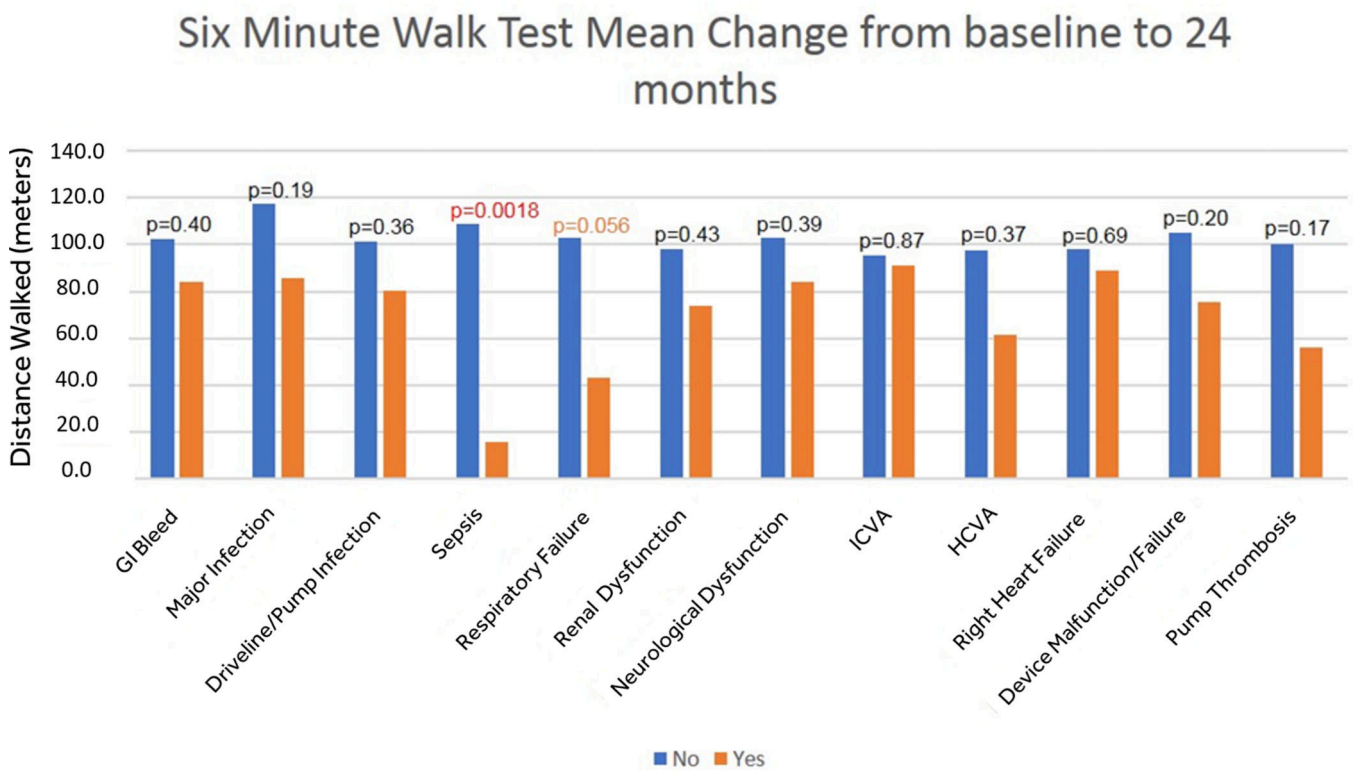

Figure 1. Six Minute Walk Distance Mean Change From Baseline to 24 Months

Mean change from baseline to 24 months in 6 minute walk test, stratified by adverse event type. GI = gastrointestinal, iCVA = ischemic cerebrovascular accident (stroke), hCVA = hemorrhagic cerebrovascular accident (stroke).

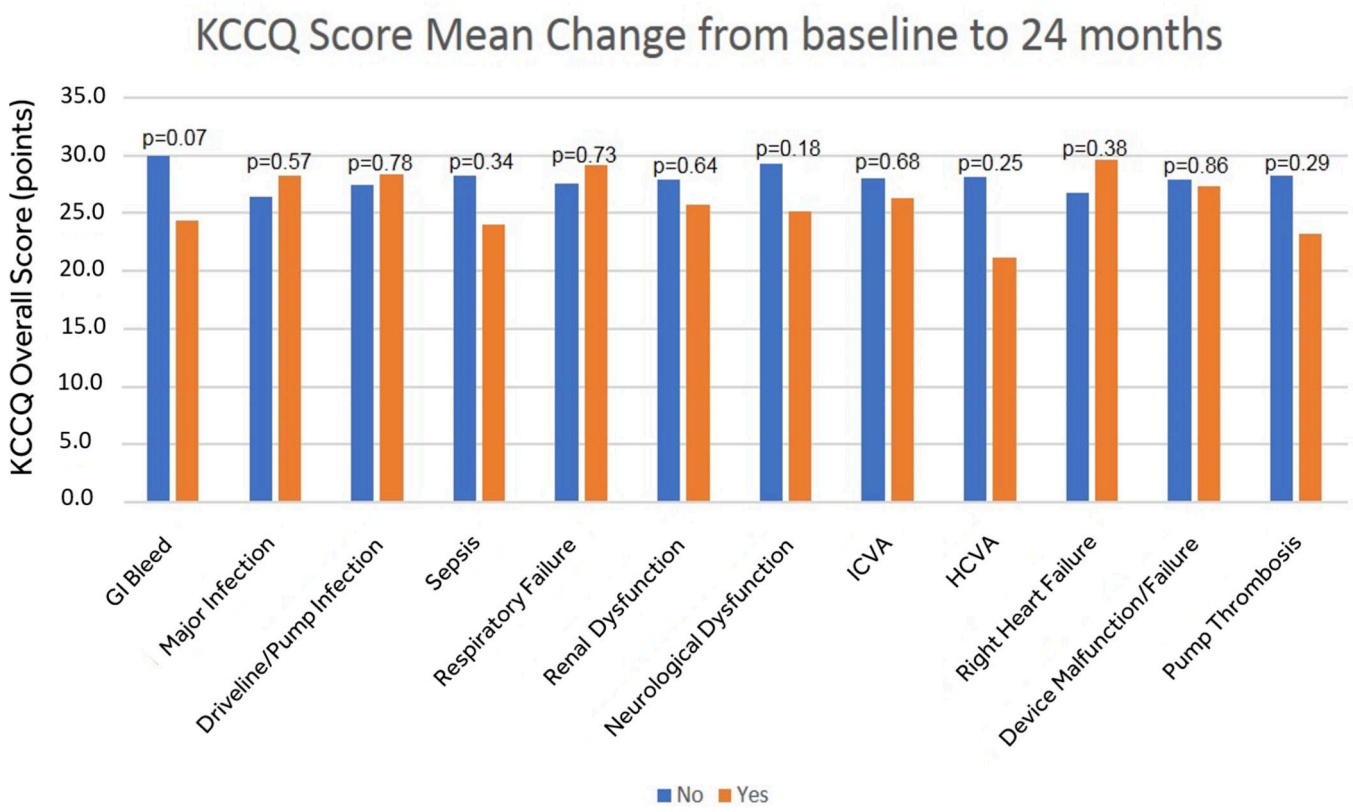

Figure 2. KCCQ Score Mean Change from Baseline to 24 Months

Mean change from baseline to 24 months in Kansas City Cardiomyopathy Questionnaire score, stratified by adverse event type. GI = gastrointestinal, iCVA = ischemic cerebrovascular accident (stroke), hCVA = hemorrhagic cerebrovascular accident (stroke).

Table I.

Baseline characteristics for patients stratified by degree of improvement

	KCCQ Change from baseline to 2 years				6MWT Change from baseline to 2 years			
	<20 (n=103)	**20–40 (n=80)**	**>40 (n=89)**	**p-value**	**≤0 (n=98)**	**1–199 (n=95)**	**>200 (n=70)**	**p-value**
Age, years	64.4 ± 11.6	63.3 ± 11.3	61.7 ± 14.1	0.30	65.9 ± 8.6	63.0 ± 12.6	59.9 ± 14.1	0.005
Male Gender	83.5%	73.8%	78.7%	0.28	70.4%	80.0%	80.0%	0.22
Race, %				0.79				0.78
White	73.8%	68.8%	75.3%		73.5%	71.6%	68.6%	
Black	22.3%	27.5%	23.6%		22.4%	24.2%	30.0%	
Hispanic/other	3.9%	3.7%	1.1%		4.1%	4.2%	1.4%	
BMI, kg/m ^{2}	28.8 ± 6.3	27.6 ± 5.8	27.5 ± 5.7	0.23	28.9 ± 6.2	28.1 ± 5.9	26.8 ± 5.9	0.09
Ischemic Cardiomyopathy	59.2%	46.3%	51.7%	0.22	55.1%	57.9%	48.6%	0.49
Previous Stroke	12.6%	12.5%	11.2%	0.95	9.2%	10.5%	15.7%	0.41
History of Diabetes	46.6%	43.8%	48.3%	0.83	51.0%	42.1%	44.3%	0.44
Treated for HTN	78.6%	63.8%	67.4%	0.06	66.3%	76.8%	67.1%	0.22
Creatinine, umol/liter	119.5 ± 36.1	123.5 ± 38.8	115.9 ± 34.7	0.40	119.2 ± 37.0	120.3 ± 36.8	120.3 ± 38.8	0.97
Cardiac Index, L/min/m ^{2}	2.2 ± 0.7	2.2 ± 0.07	2.2 ± 0.5	0.47	2.2 ± 0.7	2.2 ± 0.6	2.1 ± 0.6	0.70
LVEDD, cm	6.9 ± 1.1	6.7 ± 1.4	7.0 ± 1.2	0.47	6.8 ± 1.2	6.8 ± 1.1	6.9 ± 9.4	0.78
Intermacs, %				0.22				0.52
1	2.0%	1.3%	4.5%		2.0%	2.1%	4.3%	
2	21.6%	32.9%	34.8%		21.4%	27.7%	40.0%	
3	44.1%	40.5%	42.7%		49.0%	44.7%	35.7%	
4–7	32.3%	25.3%	18.0%		27.6%	25.5%	20.0%	
Baseline KCCQ	49.4 ± 21.7	42.2 ± 18.6	27.0 ± 12.2	<0.001	39.1 ± 22.6	42.6 ± 17.5	37.2 ± 20.0	0.23
Baseline 6MWT	157.0 ± 142.8	144.0 ± 140.9	115.7 ± 123.5	0.13	147.7 ± 142.6	181.5 ± 124.4	35.6 ± 83.7	<0.001

Legend: HTN=hypertension, KCCQ = Kansas City Cardiomyopathy Questionnaire, 6MWT = 6 minute walk test, LVEDD = left ventricular end-diastolic dimension

Table II.

Adverse Events up to 2 Years Post-Implant

	Change from Baseline to 2 years: 6MWT			
	≤0 meters (n=98)	**1–199 meters (n=95)**	**>200 meters (n=70)**	**p-value**
Number of Major Adverse Events	4.92 ± 3.48	4.04 ± 3.30	3.39 ± 2.43	0.008
	Change from Baseline to 2 years: KCCQ			
	<20 points (n=103)	**20–40 points (n=80)**	**>40 points (n=89)**	**p-value**
Number of Major Adverse Events	4.32 ± 3.35	3.68 ± 2.30	3.46 ± 2.69	0.10

Legend: KCCQ, Kansas City Cardiomyopathy Questionnaire; 6MWT, 6-minute walk test