Medical therapy in heart failure before and after left ventricular assist device implantation

Rafał Dąbrowski, Edyta Smolis-Bąk, Ilona Kowalik, Jarosław Szymański, Krzysztof Kuśmierski, Jarosław Kuriata, Krzysztof Jaworski, Tomasz Chwyczko, Przemysław Leszek, Tomasz Zieliński, Ryszard Piotrowicz, Piotr Kołsut

National Institute of Cardiology, Warszawa, Poland

Correspondence to:
Rafał Dąbrowski, MD, PhD, Department of Coronary Artery Disease and Cardiac Rehabilitation, National Institute of Cardiology, Alpejska 42, 04–628 Warszawa, Poland,
phone: +48 343 44 09,
e-mail: rdabrowski45@gmail.com, rdabrowski@ikard.pl

DOI: 10.33963/v.kp.98042

Received:
July 11, 2023

Accepted:
October 30, 2023

Early publication date:
November 14, 2023

INTRODUCTION

Since their introduction in 2000, left ventricular assist devices (LVADs) have become an important treatment option for patients with heart failure with reduced ejection fraction (HFrEF). However, after LVAD implantation as a bridge to candidacy, recovery, transplantation, or destination therapy, patients require continuation of optimal medical therapy (OMT) [1]. So far, expert positions on heart failure (HF) permanent medical therapy have not focused on patients with LVADs [1–4].

The study aimed to compare medical therapy in patients before and after (at discharge) LVAD implantation.

METHODS

We included in this prospective single-center study all consecutive patients who were undergoing rehabilitation after LVAD implantation (Jan 1, 2019–Dec 31, 2021) at the Department of Coronary Artery Disease and Cardiac Rehabilitation, National Institute of Cardiology, Warsaw. Patients had implanted HeartMate3 and HVAD™ Systems (till June 3, 2021). Demographic, clinical characteristics, and medical therapy of HF were analyzed before and on discharge from the hospital. The analyzed data were obtained on an ongoing basis from hospital medical records. The study was supported by the State Committee for Scientific Research (STRATEGMED2/266798/15/NCBIR/2015). Bioethical Committee approval was issued on April 2, 2019 (IK-NPIA-0021-55/1784/2019).

Statistical analysis

In the statistical analysis, the results of continuous variables were presented in the forms of arithmetic means and standard deviations (normal distributions) or medians and quartiles (skewed distributions). Qualitative variables were reported as counts and percentages. McNemar's test (binary variables) or symmetry tests (nominal variables with 3 categories) were used to compare the significance of differences in treatment changes before and after the procedure. Two-sided testing was applied, and a P <0.05 was considered statistically significant. The analysis was performed using the SAS 9.4 statistical package (SAS Institute, NC, US).

RESULTS AND DISCUSSION

The study included 55 men with HFrEF, New York Heart Association class IV, after LVAD implantation. The mean age was 55.5 (10.7) years; left ventricular ejection fraction was 15.8 (4.6)%. The median length of hospital stay was 31 (24–43) days. Medical history included coronary artery disease: 31 patients (56.4%), valvular heart disease: 8 (14.5%), ventricular tachycardia/fibrillation: 37 (67.3%), atrial fibrillation: 35 (63.6%), cardiac resynchronization therapy: 11 (20%), implantable cardioverter-defibrillator: 50 (90.9%), stroke: 11 (20%), peripheral artery disease: 11 (20%), arterial hypertension: 34 (68%), diabetes: 21 (38.2%). Median creatinine concentration was 1.23 (0.94–1.97) mg/dl (Supplementary material, *Table S1*).

There were no changes before and after LVAD implantation in (1) use of beta-blockers (BB) –53 patients (96.4%) used them before LVAD implantation vs. 54 (98.2%) after the procedure (P = 0.56), (2) use of mineralocorticoid receptor antagonists (MRA): 53 patients (96.4%) vs. 50 (90.9%); P = 0.08,

Table 1. Medical therapy before and after LVAD implantation (n = 55)

	Before implantation	After implantation	*P*-value McNemar test	Drug withdrawal after implantation[a]	Drug initiation[b]
Beta-blockers	53 (96.4)	54 (98.2)	1.00	1 (1.9)	2 (3.7)
MRA	53 (96.4)	50 (90.9)	0.25	3 (5.7)	0 (0)
ACEI	33 (60.0)	16 (29.1)	<0.001	17 (51.5)	0 (0)
ARB	16 (29.1)	33 (60.0)	<0.001	2 (12.5)	19 (57.6)
VKA	30 (54.5)	48 (87.3)	<0.001	4 (13.3)	22 (45.8)
ASA	27 (49.1)	49 (89.1)	<0.001	2 (7.4)	24 (49.0)
Clopidogrel	1 (1.8)	1 (1.8)	1.00	1 (100)	1 (100)
Heparin	8 (14.5)	6 (10.9)	0.59	8 (100)	6 (100)
Loop diuretics					
0 (none)	3 (5.4)	9 (16.3)	0.09	9 (17.3)	3 (6.5)
1 (one)	27 (49.1)	31 (56.4)			
2 (two)	25 (45.5)	15 (27.3)			
Thiazide diuretics	11 (20.0)	0 (0)	0.004	11 (100)	0 (0)
Valsartan/sacubitril	4 (7.3)	2 (3.6)	0.50	2 (50.0)	0 (0)
SGLT-2i	1 (1.8)	2 (3.6)	1.00	0 (0)	1 (50.0)
Digoxin	9 (16.4)	8 (14.5)	0.80	8 (88.9)	7 (87.5)
Ivabradine	7 (12.7)	5 (9.1)	0.69	4 (57.1)	2 (40.0)
Amiodarone	17 (30.9)	7 (12.7)	0.012	13 (76.5)	3 (42.9)
Propafenone	1 (1.8)	1 (1.8)	1.00	1 (100)	1 (100)
Mexiletine	3 (5.4)	2 (3.6)	1.00	2 (66.7)	1 (50.0)
Sildenafil	11 (20.0)	18 (32.7)	0.13	7 (63.6)	14 (77.8)
Thyroxine	7 (12.7)	10 (18.2)	0.25	0 (0)	3 (30.0)
Metformin	10 (18.2)	9 (16.4)	1.00	3 (30.0)	2 (22.2)
Insulin	2 (3.6)	2 (3.6)	1.00	0 (0)	0 (0)
Allopurinol	30 (54.5)	38 (69.1)	0.045	4 (13.3)	12 (31.6)
Iron	8 (14.5)	9 (16.4)	0.80	7 (87.5)	8 (88.9)
Antidepressants	7 (12.7)	18 (32.7)	0.012	4 (57.1)	15 (83.3)
IPP	33 (60.0)	48 (87.3)	0.002	4 (12.1)	19 (39.6)

Data are presented as numbers (percentage). [a]Percentages in relation to the number of patients taking a given drug before implantation. [b]Percentages relative to the number of patients taking a given drug after implantation

Abbreviations: ACEI, angiotensin-converting enzyme *inhibitors;* ARB, angiotensin receptors blockers; ASA, acetylsalicylic acid; MRA, mineralocorticoid receptor antagonists; PPI, proton-pump inhibitors; SGLT-2i, sodium-glucose cotransporter 2 inhibitors; VKA, vitamin K antagonists

(3) loop diuretics, 1 or 2: 52 patients (94.6%) vs. 46 (83.7%); $P = 0.09$ — with tendency to reduce, (4) digoxin: 9 patients (16.4%) vs. 8 (14.5%); $P = 0.80$. The number of patients treated with sacubitril/valsartan was low: 4 (7.3%) before vs. 2 (3.6%) after the procedure; $P = 0.16$. There was a reduction in using (1) angiotensin-converting enzyme inhibitors (ACEI): 33 patients (60.0%) before vs. 16 (29.1%) after the procedure; $P < 0.001$, (2) thiazide diuretics: 11 patients (20%) before vs. 0 (0%) after the procedure; $P = 0.004$, and (3) amiodarone: 17 patients (30.9%) before vs. 7 (12.7%) after the procedure; $P = 0.012$.

At discharge, there was, however, an increase in the use of (1) angiotensin receptor blockers (ARB): 16 patients (29.1%) vs. 33 (60.0%); $P < 0.001$, (2) allopurinol 30 (54.5%) vs. 38 (69.1%); $P = 0.045$, and (3) proton-pump inhibitors: 33 (60%) vs. 48 (87.3%); $P = 0.002$. The number of patients receiving vitamin K antagonists increased: 30 (54.5%) vs. 48 (87.3%); $P < 0.001$, so did the number of patients taking aspirin: 27 (49.1%) vs. 49 (89.1); $P < 0.001$, due to implanted devices (Table 1). No adverse events that would cause withdrawal from any drug have been observed. There were no deaths during hospitalization.

The new findings of the current report are that HF optimal treatment in accordance with the guidelines, which includes the basic drug groups: BB, ACEI/ARB, MRA, and loop diuretics despite LVAD implantation was continued and ACEI usage was reduced in favor of the ARB, probably due to better tolerance. Continuation of treatment with loop diuretics despite improvement of left ventricular hemodynamic parameters may be surprising, but 56% of patients had chronic kidney disease (mean eGFR 49.1 ml/min, standard deviation 16). According to the 2019 European Association for Cardio-Thoracic Surgery Expert Consensus on long-term mechanical circulatory support, many patients still suffer from volume overload after LVAD implantation and require diuretic therapies [5]. During the study period, sodium-glucose cotransporter 2 inhibitors were not routinely used due to their limited availability and publication of the guidelines for their use only in the final phase of the study [2]. Despite a lack of well-controlled data, there are potential benefits of HFrEF OMT in LVAD patients to improve, among others, pulmonary circulation conditions, right ventricular support, and to reduce atrial and ventricular arrhythmias. Compared to other published retrospective studies, in our study the percentage of patients treated in the same way as before LVAD implantation was significantly higher. There were no significant differences in the treatment modes before

and after the procedure except for more frequent use of ARB and a reduction in the use of thiazide diuretics and amiodarone. Continued use of BB is important to reduce the risk of arrhythmia and control blood pressure. The reduced use of ACEI in favor of the ARB was probably due to better ARB tolerance and the growing use of valsartan in combination with sacubitril [3]. Continuation of MRA treatment is important in terms of inhibiting fibrosis, further remodeling of heart chambers, and reducing arrhythmias. Due to LVAD implantation, all patients received optimal anticoagulation (10.9% temporarily on heparin) and antiplatelet therapy.

The actual guidelines for the treatment of HF do not refer directly to the further medical treatment of LVAD patients in general because there have been no prospective studies on medical therapy in this group of patients so far [3, 4]. Continuing medical treatment in patients with cardiomyopathy of non-ischemic etiology has a key role in restoring the function of the cardiac muscle (class I C recommendation) [5]. HF medications (ACEI/ARB, BB, MRA, loop diuretics) should be considered during mechanical circulatory support (class IIa C recommendation) [5]. However, considering numerous comorbidities, such as cardiac arrhythmias, chronic kidney disease, liver failure, and others, OMT may be limited [6]. Treatment limitations may also result from improvement of the patient's hemodynamic status and prevention of excessive hypotension.

An analysis of 5840 LVAD recipients demonstrated that the use of ACEI/ARB was 53%, BB: 72%, loop diuretics: 66%, and MRA: only 34.4% at 6 months post implantation. Use of OMT (ACEI/ARB, MRA, BB) was higher for those implanted in more recent years [7]. Continued treatment for HF after surgery may improve the prognosis of LVAD patients. In a report of 12 144 durable-LVAD recipients, those receiving any neurohormonal blockade with either ACEI/ARB, BB, or MRA had significantly improved survival at 4 years postimplantation compared to those on no therapy (respectively: 56.0%; 95% confidence interval [CI], 54.5%–57.5% vs. 43.9%; 95% CI, 40.5%–47.7%). Patients on all three therapies had the lowest hazard of death compared to other groups (HR, 0.34; 95% CI, 0.28–0.41). Also, quality of life and functional status were improved with neurohormonal blockade [8]. According to some authors, the role of optimal treatment (LBA, ACEI/ARB, MRA, sacubitril/valsartan, sodium-glucose cotransporter 2 inhibitors, diuretics) in LVAD patients is not fully established [9]. Although, the 2023 International Society for Heart and Lung Transplantation Guidelines finally recommend neurohormonal blockade and the treatment of hypertension after LVAD implantation with ACEI, ARB, ARB-neprilysin inhibitors, BB, and MRA (class I B recommendation [10]), which confirms our results.

CONCLUSIONS

Left ventricular assist device implantations do not significantly change modes of medical therapy in HF, including drugs that improve prognosis. Interestingly, the use of ACEI has been significantly reduced in favor of the ARB probably due to better tolerance. This observation requires further studies.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

REFERENCES

1. Tycińska A, Grygier M, Biegus J, et al. Mechanical circulatory support. An expert opinion of the Association of Intensive Cardiac Care and the Association of Cardiovascular Interventions of the Polish Cardiac Society. Kardiol Pol. 2021; 79(12): 1399–1410, doi: 10.33963/KP.a2021.0169, indexed in Pubmed: 34861044.
2. Rosano GMC, Moura B, Metra M, et al. Patient profiling in heart failure for tailoring medical therapy. A consensus document of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2021; 23(6): 872–881, doi: 10.1002/ejhf.2206, indexed in Pubmed: 33932268.
3. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur J Heart Fail. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022; 145(18): e895–e1032, doi: 10.1161/CIR.0000000000001063, indexed in Pubmed: 35363499.
5. Potapov EV, Antonides C, Crespo-Leiro MG, et al. 2019 EACTS Expert Consensus on long-term mechanical circulatory support. Eur J Cardiothorac Surg. 2019; 56(2): 230–270, doi: 10.1093/ejcts/ezz098, indexed in Pubmed: 31100109.
6. Correale M, Paolillo S, Mercurio V, et al. Non-cardiovascular comorbidities in heart failure patients and their impact on prognosis. Kardiol Pol. 2021; 79(5): 493–502, doi: 10.33963/KP.15934, indexed in Pubmed: 34125921.
7. Khazanie P, Hammill BG, Patel CB, et al. Use of heart failure medical therapies among patients with left ventricular assist devices: insights from INTERMACS. J Card Fail. 2016; 22(9): 672–679, doi: 10.1016/j.cardfail.2016.02.004, indexed in Pubmed: 26892975.
8. McCullough M, Caraballo C, Ravindra NG, et al. Neurohormonal blockade and clinical outcomes in patients with heart failure supported by left ventricular assist devices. JAMA Cardiol. 2020; 5(2): 175–182, doi: 10.1001/jamacardio.2019.4965, indexed in Pubmed: 31738366.
9. Hollis IB, Doligalski CT, Jennings DJ. Pharmacotherapy for durable left ventricular assist devices. Pharmacotherapy. 2021; 41(1): 14–27, doi: 10.1002/phar.2491, indexed in Pubmed: 33278842.
10. Saeed D, Feldman D, Banayosy AEl, et al. The 2023 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: A 10-year update. J Heart Lung Transplant. 2023; 42(7): e1–e222, doi: 10.1016/j.healun.2022.12.004, indexed in Pubmed: 37245143.