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Sacubitril-Valsartan in LVAD Patients: Potentials for the Future?

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Abstract

Beneficial effects of Angiotensin Receptor Neprilysin Inhibitors (ARNIs) in heart failure patients are increasingly being recognized. Current literature on ARNIs among LVAD patients is based on small retrospective studies; however, these reports suggest their acceptable tolerability, effective blood pressure control and improvement in NT-proBNP levels. As we continue to better understand their cardio-protective effects including potential of myocardial recovery their use in patients with LVADs is bound to increase. Side effects that may limit their tolerability include acute kidney injury, hypotension, hyperkalemia and angioedema. Clinical trials are ongoing to assess their safety and tolerability in LVAD patients.

Keywords: ARNI; Efficacy; LVAD; Safety; Sacubitril-Valsartan

Manuscript

Sacubitril-Valsartan is the most commonly used Angiotensin Receptor Neprilysin Inhibitor (ARNI) which is now a front-line pharmacological therapy for heart failure with reduced ejection fraction. Sacubitril inhibits neprilysin, an endopeptidase that breaks down several vasoactive peptides- including natriuretic peptides, bradykinin, and adrenomedullin. Increased levels of these vasoactive peptides counteract the neurohormonal activation that contribute to cardiac remodeling in heart failure. Valsartan is an Angiotensin Receptor Blocker (ARB) that antagonizes angiotensin- 1 (AT-1) which inhibits the Renin-Angiotensin Activation System (RAAS), also known for its detrimental cardiac remodeling effects in the heart. The Paradigm HF trial showed Sacubitril-Valsartan was superior to Valsartan in reducing hospitalization and death from cardiovascular causes [1]. In the Pioneer HF trial, initiation of Sacubitril-Valsartan during hospitalization with decompensated heart failure resulted in a greater reduction of NT-proBNP concentration than Enalapril alone, without a significant increase in rates of adverse events [2]. In a study by Martens et al., there was a reduction in Ventricular Tachycardia/Ventricular Fibrillation (VT/VF) burden, Non-Sustained Ventricular Tachycardia (nsVT) burden, and Premature Ventricular Contractions (PVCs) after initiation of Sacubitril-Valsartan compared to ACE-i/ARBs alone in heart failure patients, which was attributed to improvement in cardiac function due to reverse cardiac remodeling. LVEF improved in 44% of patients after initiation of Sacubitril-Valsartan by at least 5%. The authors suggested that the reduction in sudden cardiac deaths seen in the Paradigm HF trial (particularly in patients with non-ischemic cardiomyopathy) could partially be linked to the reduction in the ventricular tachyarrhythmias after initiation of the drug [3,4]. An important effect of Sacubitril-valsartan compared to Enalapril was a reduction in the profibrotic biomarkers studied by Zile et al [5]. Initiation of Sacubitril-Valsartan during hospitalization in patients with heart failure with

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Samiullah Arshad et al., Cardiol Cardiovasc Med 2022
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reduced ejection fraction is predicated to be cost-effective than starting as an outpatient or continued use of enalapril [7]. In patients with LVADs, continuous flow without pulsatility triggers RAAS with aggressive pharmacological therapy targeting RAAS inhibition is known to result in myocardial recovery and successful explantation of LVADs [7]. Vaidya et al. have shown that the use of ACE-i/ARBs in LVAD patients significantly reduced ProBNP levels at six months and twelve months and improved survival [8]. In addition to promoting myocardial recovery, ACE-i/ARBs have reduced the risk of gastrointestinal bleeding and AV-malformations among LVAD patients [9]. The question then arises, does sacubitril-valsartan impart the above benefits among patients with LVADs? A literature search conducted on PubMed, Google Scholar, and SCOPUS for terms related to 'sacubitril-valsartan' and 'LVAD' revealed ten retrospective cohort studies and one prospective cohort study with a combined total of 628 patients. The literature search was conducted from July 10th 2022. The primary outcome consistently assessed throughout all but one study (Schnettler et. al.) was reduction in mean arterial pressure (MAP). Nine of the ten studies that reported this outcome found a significant reduction of MAP with initiation of sacubitril-valsartan, ranging from 5 mmHg to 20 mmHg. In addition to MAP reduction, Dobarro et. al reported a significant reduction in NT-proBNP levels following ANRI initiation of 1,466 pg/ml [13]. Study by Alishetti et. al also found a reduction in NT-proBNP of 501 pg/ml [17]. Six of the eleven studies reported the types of LVADs in the patients. Follow up time throughout these studies ranged from 3 months to 27.5 months. Adverse effects related to sacubitril-valsartan initiation in LVAD patients were rare and included hyperkalemia, symptomatic hypotension, allergic reaction/angioedema, and acute kidney injury. Among the 628 total patients, the most common adverse effect was symptomatic hypotension as reported in 61 patients (10%). In addition, there were 6 reports (1%) of hyperkalemia, 1 (0.01%) report of acute kidney injury, 9 (2%) reports of allergic reactions. Details of each study have been provided in table 1.

Table 1: Literature Review of Studies With Use of ARNI's among LVAD Patients.

Authors	Study	Study Design	Control?	Number of Patients	Type of LVAD	Duration of therapy/ Follow up	Improvement in MAP?	Adverse Effects
Freed et. al [10]	Sacubitril-Valsartan Improves Blood Pressure and Heart Failure in Left Ventricular Assist Device (LVAD) Patients-(2020)	Retrospective cohort study	None	20	Not described	3 months	Yes (reduced by 17 mmHg)	Yes (dizziness/ hypotension- 3; LVAD suction- 1; cough- 1)
Straw et. al [11]	Successful Use of Sacubitril/Valsartan in Patients with a Left Ventricular Assist Device (2020)	Longitudinal, retrospective cohort study	None	9	All 3 commercially available LVADs were evenly represented	1 month and last follow up	Yes (reduced by 18 mmHg)	None
Randhawa et. al [12]	Sacubitril-Valsartan Initiation Post-Left Ventricular Assist Device is Safe and Effective (2019)	Retrospective cohort study	None	10	Continuous flow LVAD	Not described	Yes (reduced by 20 mmHg)	Yes (hyperkalemia- 1)
Dobarro et. al [13]	Use of sacubitril-valsartan in blood pressure control with left ventricular assist devices (2020)	Retrospective cohort study	None	22	HeartMate3, HeartWare HVAD1	9-27.5 months	Yes (reduced by 5 mmHg)	Yes (symptomatic hypotension- 1)
Sharma et. al [14]	Tolerability of Sacubitril/ Valsartan in Patients With Durable Left Ventricular Assist Devices (2020)	Retrospective cohort study	None	5	HeartMate3, HeartWare HVAD1	1 month and last follow up	Yes (reduced by 20 mmHg)	Yes (AKI- 1; symptomatic hypotension- 2)
Nicolsen et. al [15]	Sacubitril-Valsartan versus Standard Anti-Hypertensives in Left Ventricular Assist Device Patients (2018)	Retrospective cohort study	None	26	HeartMate2	Not described	Yes (reduced by 20 mmHg)	None

Samiullah Arshad et al., Cardiol Cardiovasc Med 2022
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Njue et. al [16]	Neurohormonal Blockade with Sacubitril/Valsartan in Left Ventricular Assist Device (LVAD) Patients (2018)	Prospective cohort study	None	15	Not described	3 months	No	None
Alishetti et. al [17]	Angiotensin receptor neprilysin inhibitor use in patients with left ventricular assist devices: A single-center experience	Retrospective cohort study	None	30	Not described	6 months	N/A	None
Straw et. al [18]	Safety and Effectiveness of Sacubitril/Valsartan in Patients with a Left Ventricular Assist Device (2021)	Longitudinal, retrospective cohort study	None	46	Not described	21 months	Yes (reduced by 12 mmHg)	Yes (symptomatic hypotension- 3; itching- 1; epistaxis- 1)
Roberts et. al [19]	Sacubitril/Valsartan Improves Outcomes in Left Ventricular Assist Device Recipients (2022)	Longitudinal, retrospective cohort study	None	188	Not described	24 months	Yes (reduced by 8 mmHg)	None
Schnettler et. al [20]	Safety of Contemporary Heart Failure Therapy in Patients with Continuous-Flow Left Ventricular Assist Devices (2020)	Retrospective cohort study	Yes- 83 patients after propensity score matching	257	HeartWare, HeartMate3	12 months	N/A	Yes (hyperkalemia- 5; AKI- 17; symptomatic hypotension- 52; allergies/ angioedema- 8; GI problems- 3)

With the approval of Sacubitril-Valsartan in 2015 by FDA for systolic heart failure patients, and with its increasing identified benefits, it will find its way in LVAD patients. Sacubitril-Valsartan has a role in remodeling of cardiac tissue, reduction in NT-proBNP levels, prevention of ventricular arrythmias, and improvement in the pump flow with blood pressure control when compared to standard therapies in heart failure patients, with a potential of reducing the number of hospital readmissions as well as stroke among LVAD patients. Further, reduction of arrhythmias in general heart failure patients may be of significant importance among LVAD patients. Its role in conserving the kidney function in patients of systolic heart failure makes it superior to ACE-I alone. In our opinion, it would be safe to extrapolate the beneficial effects of ARNIs to LVAD patients, and it is possible that their use in the early post-implantation phase may significantly impact outcomes. Although the long-term implications of ARNIs among LVAD patients are unknown, it is an avenue worth exploring. Notable barriers to generalized utility would include known side effects – acute kidney injury, hypotension, hyperkalemia and risk of angioedema. Two prospective clinical trials (NCT04103554 and NCT04191681) are currently underway to assess the safety and tolerability of Sacubitril-Valsartan among LVAD.

Conflicts of Interest

The authors report no conflicts of interest.

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Samiullah Arshad et al., Cardiol Cardiovasc Med 2022
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