Lavare Cycle in Patients Receiving HeartWare Left Ventricular Assist Device

NCT04199793

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Protocol Title: Assessment of LAVARE™ cycle implementation among patients following HeartWare left ventricular assist device implantation: A prospective randomized controlled pilot study

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1.0 Background

Left ventricular assist device (LVAD) patients remain at risk for pump thrombus and thromboembolic events through multiple mechanisms. The HeartWare® Ventricular Assist System (HVAD®, HeartWare Inc., Framingham, MA, USA) includes a novel speed modulation feature called Lavare™ cycle. It consists of 3 phases: phase 1 – a 200 rpm decrease from baseline speed for 2 seconds, phase 2 – a 100 rpm increase from baseline for 1 second and phase 3 – return of speed to baseline; this cycle repeats itself once every minute. The Lavare™ Cycle is aimed to promote washing of left ventricle to decrease blood stasis and subsequent risk of thrombus formation, ingestion and/or expulsion. In a post-hoc analysis of ReVOLVE registry, which includes 248 patients implanted with the HVAD following Conformité Européenne Mark in nine centers in Europe and Australia, no adverse impact on survival was observed with Lavare™ cycle. Additionally, lower risk of stroke, sepsis and right heart failure was observed among those with Lavare™ cycle in the abovementioned study. However, no prior study has prospectively evaluated the impact of Lavare™ cycle on patient outcomes in a randomized fashion.

2.0 Rationale and Specific Aims

Primary objective: To assess feasibility of conducting a future larger trial that investigates whether, among patients receiving HeartWare LVAD, Lavare cycle results in lower risk of pump-related complications.

Outcomes of interest:

1. **Primary**
    - **a.** Composite endpoint of total ischemic events, thrombotic or thromboembolic events/Pump Hemolysis/Pump Thrombosis/ Pump exchange
2. **Secondary**
    - a. All-cause mortality
    - b. Survival to transplantation
    - c. LVAD related complications
        - i. Stroke
        - ii. Transient ischemic attack
        - iii. Mucocutaneous bleeding
        - iv. Right ventricular failure
        - v. Infection: LVAD system related
        - vi. Moderate or Severe aortic insufficiency
    - d. Changes in biomarkers

e. Re-hospitalizations
f. Echocardiographic changes in myocardial structure and function
g. Functional status
    i. NYHA functional class
    ii. 6-minute walk test
h. Quality of life
    i. KCCQ

Design: This is a pilot 2-arm prospective randomized controlled trial. Both treatment strategies, Lavare cycle on and off, are consistent with standard of care.

Study Population: This trial will enroll patients undergoing their first HeartWare LVAD implantation as well as those chronically supported with HeartWare LVAD. Clinical data will be collected at baseline and at regular post-enrollment follow-up until trial ends. For chronically supported patients, minimum support duration of 3-months will be required.

Duration of follow-up: 180-days; follow-up visits will be logged at 30-days, 90-days and 180-days.

3.0 Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Age ≥18 years
2. Approved for or supported with HeartWare durable left ventricular assist device
3. Capable of giving informed consent

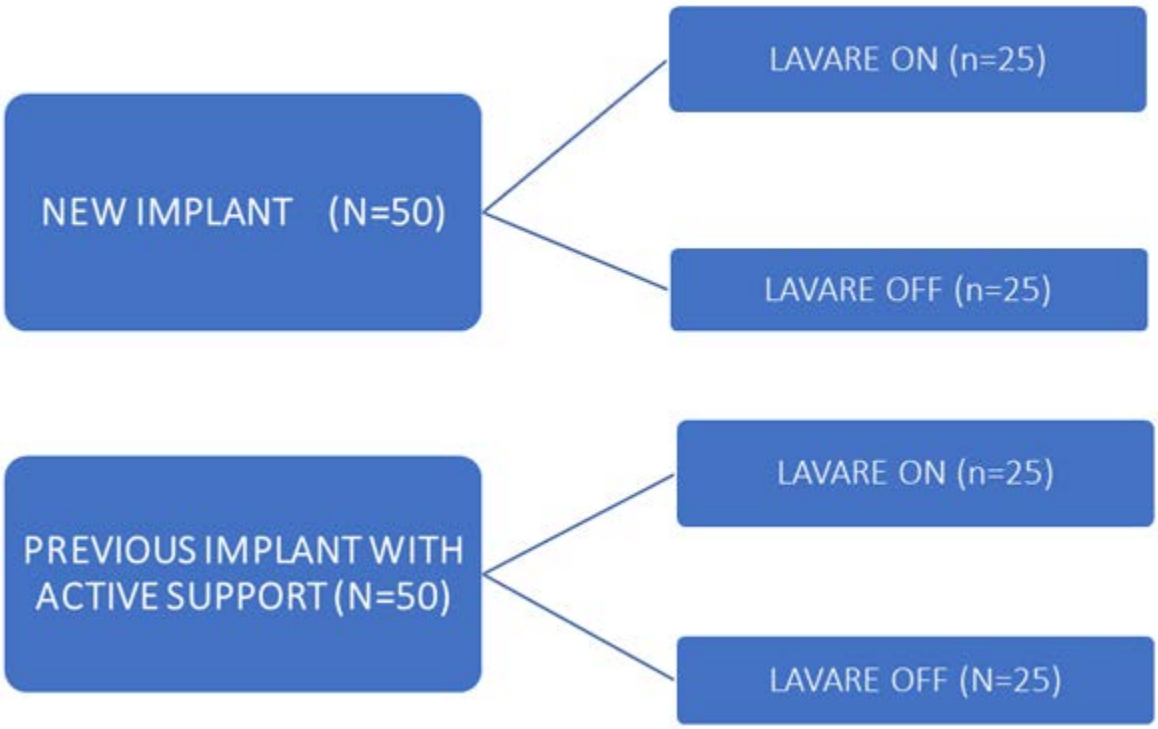
Exclusion Criteria:

1. **New implantation:**
    a. Age <18 years
    b. INTERMACS profile 1 at the time of implantation
    c. Presence of intra-cardiac thrombus
    d. History of thromboembolic event within previous 3 months of enrollment
    e. Chronic Kidney disease stage 4 or 5, or on any form of dialysis (eGFR must be consistently documented <30 for 30 days)

2. **Previous HeartWare implant with active support:**
    a. Support duration <3 months
    b. History of prior LVAD pump exchange
    c. History of LVAD pump hemolysis or thrombosis as defined by INTERMACS criteria
    d. History of stroke or transient ischemic event within previous 3 months of enrollment
    e. History of post-LVAD severe right ventricular failure as defined by INTERMACS criteria within previous 3 months of enrollment
    f. History of pump-related infection treated within previous 3 months of enrollment or those on chronic antibiotics suppressive therapy for pump related infection
    g. History of post-LVAD intra-cardiac or arterial thrombus or thromboembolic event within previous 3 months of enrollment
    h. INR <2 within previous 30-days from the date of enrollment
    i. Aspirin dose <325 mg/day
    j. LDH levels ≥ 3 times the upper normal limit in previous 3 months
    k. Chronic kidney disease stage 4 or5, or any form of dialysis (eGFR must be consistently documented <30 for 30 days).

4.0 Enrollment/Randomization

Number of subjects: N=100; 50 patients undergoing their first HeartWare LVAD implantation and 50 patients with chronic HeartWare LVAD support will be included. This multi-center study will be conducted at up to 4 sites.



Procedures for randomization

Using REDCap, participants will be randomly assigned in a 1:1 ratio. Participants will receive a randomization number. The randomization number identifies the participant for all procedures occurring after randomization. Once a randomization number is assigned to a participant, it cannot be re-assigned to another participant.

There are 2 arms:

1) Lavare™ Cycle - On
   OR
2) Lavare™ Cycle – Off

5.0 Study Procedures

Screening Visit: Visit 1 (prior to new LVAD implantation for New Implants and at the time of consent for Previous Implants)

- Informed Consent
- Demographics
- Review of Medical History
- Blood sampling for biomarkers (approximately 20mLs)
- KCCQ questionnaire
- 6-minute walk test (Can be deferred if patient is on inotropic or MCSD support)
- NYHA functional class assessment defined as follows:

1. Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
2. Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3. Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest.
4. Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
5. No NYHA class listed or unable to determine.

Data will be collected on the following tests that were likely performed as part of the standard LVAD evaluation. The participant will not be required to undergo these tests for the purposes of this trial:

- Echocardiogram
- Right heart catheterization or Swan-Ganz Catheterization

The Screening Visit and the Randomization Visit can occur on the same day, if all study criteria have been met.

The following will happen:

- Randomization: Randomly assigned by REDCap to one of the two groups:
  1Lavare™ Cycle - On
  OR
  2 Lavare™ Cycle – Off
- Study intervention: Changes in Lavare™ Cycle will be made by the study staff according to the group you are assigned.
- LVAD data: standard parameters displayed on the screen upon routine interrogation of the LVAD will be collected.

Visit 2: Day 30 (+/- 14 Days)

- Review of Medical History
- Blood sampling for biomarkers
- 6-minute walk test (Can be deferred if patient is on inotropic or MCSD support)
- NYHA functional class assessment defined as follows:

1. Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
2. Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3. Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest.
4. Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
5. No NYHA class listed or unable to determine.

- LVAD data: Standard parameters displayed on the screen upon routine interrogation of the LVAD will be collected. We will also ask Medtronic to provide trends in the LVAD parameters over past 30 days utilizing log-files that are stored in their data bank. **Please send log-files to Medtronic with a title: Lavare Trial Log-Files for appropriate storage and analysis.**
- Adverse Events

Data will be collected on the following tests that were likely performed as part of the standard LVAD evaluation. The participant will not be required to undergo these tests for the purposes of this trial:

- Echocardiogram
- Right heart catheterization or Swan-Ganz Catheterization

Visit 3: Day 90 (+/- 14 Days)

- Review of Medical History
- Blood sampling for biomarkers (approximately 20 mLs)
- KCCQ questionnaire
- 6-minute walk test (Can be deferred if patient is on inotropic or MCSD support)
- NYHA functional class assessment defined as follows:

1. Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
2. Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3. Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest.
4. Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
5. No NYHA class listed or unable to determine.

- LVAD data: Standard parameters displayed on the screen upon routine interrogation of the LVAD will be collected. We will also ask Medtronic to provide trends in the LVAD parameters over past 30 days utilizing log-files that are stored in their data bank. **Please send log-files to Medtronic with a title: Lavare Trial Log-Files for appropriate storage and analysis.**
- Adverse events

Data will be collected on the following tests that were likely performed as part of the standard LVAD evaluation. The participant will not be required to undergo these tests for the purposes of this trial:

- Echocardiogram
- Right heart catheterization or Swan-Ganz Catheterization

Visit 4: Day 180 (+/- 30 Days)

- Review of Medical History
- Blood sampling for biomarkers (approximately 20 mLs)
- KCCQ questionnaire
- 6-minute walk test (Can be deferred if patient is on inotropic or MCSD support)
- NYHA functional class assessment defined as follows:

1. Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
2. Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
3. Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m). Comfortable only at rest.
4. Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.
5. No NYHA class listed or unable to determine.

- LVAD data: Standard parameters displayed on the screen upon routine interrogation of the LVAD will be collected. We will also ask Medtronic to provide trends in the LVAD parameters over past 30 days utilizing log-files that are stored in their data bank. **Please send log-files to Medtronic with a title: Lavare Trial Log-Files for appropriate storage and analysis**.
- Adverse events

Data will be collected on the following tests that were likely performed as part of the standard LVAD evaluation. The participant will not be required to undergo these tests for the purposes of this trial:

- Echocardiogram
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Schedule of Events					
		At the time of randomization	30-day Visit (+/-14 days)	90-day Visit (+/-14 days)	180-day Visit (+/-30 days)
Demographics	Age, gender, race	x			
Comorbidities	Etiology of heart failure, Atrial arrhythmia, Ventricular arrhythmia, Hypertension, Diabetes, Hyperlipidemia, Cerebrovascular event Peripheral arterial disease, Cancer, Chronic kidney disease and its stage, Dialysis, COPD, Obesity, Presence of pacemakers/ ICD (BiV/ dual/ single), Prior cardiac surgery, History of sternotomy, Number of sternotomies, History of hypercoagulable disease, History of prior DVT, History of prior PE, History of HIT	x			
Laboratory values	Basic chemistry panel, Complete blood count with differential, Liver function test, INR, LDH, Urine analysis	x	x	x	x
Biomarkers	NT-pro-BNP, ST-2, GDF-15, Galactin-3, Hs-CRP, TNF-alpha, IL-6, NGAL, KIM-1, TIMP-2, IGFBP-7, Ang-2, Ang-1, Soluble Tie-2, VEGF, Thrombin, vWF,	x	x	x	x
Functional parameters	6-minute walk test, NYHA functional class	x	x	x	x
Echocardiogram		x	x	x	x
Review of Medical History		X	X	X	X
Pulmonary artery catheter data		x	X	X	X
VAD specific variables	Implantation indication (DT/BTT), Implant Technique (sternotomy/ thoracotomy), INTERMACS class, Inotropes (presence, types and duration), Temporary support device (presence, type and duration), diuretics (types, doses)	x			
VAD parameters	(power, PI, flow, speed, hematocrit), log-files	x	x	x	x
Quality of life	KCCQ score	x		x	x
Post Implant VAD related AE's	Arterial and venous thromboembolic events, neurological dysfunction, bleeding, pump hemolysis/thrombosis/exchange, pump malfunction, myocardial infarction, infection, right heart failure, aortic regurgitation, re-hospitalizations, cardiac arrhythmia, hypertension, major renal, respiratory or hepatic dysfunction and other major adverse events.		x	x	x

6.0 Risks

We do not have data to detail potential risks and their chances arising from participation in this study. This study aims at understanding this very question.

Hypothetically, conditions that lead to decreased blood volume in the left side of the heart (such as dehydration, excessive bleeding, right HF, fluid around the heart, etcetera) can increase the chances of suction events or low flow alarms with implementation of the Lavare™ Cycle.

1. Suction event occurs when decreased blood volume in the left side of heart causes part of left heart wall *sucked over* the LVAD pump's inflow cannula; the result of this event is reduction in LVAD pump speed to reduce the suction pressure and free up the sucked over left heart wall.
2. Low flow alarm is triggered when average flow through the pump drops below the set limit.

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Definition of Adverse Event (AE)

An AE is any untoward medical occurrence (e.g., noxious or pathological changes) in a subject compared with pre-existing conditions that may occur during any part of the clinical study. An AE is defined as being independent of assumption of any causality (e.g., primary or concomitant disease or study design). AEs are evaluated by the Investigator and maintained in the research records at the site.

Definition of Serious Adverse Event (SAE)

An SAE is an AE occurring during any study phase (i.e., run-in, treatment, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Procedures for Reporting Adverse Events (AEs)

All SAEs are be reported to the Vanderbilt University Medical Center (VUMC) Clinical Research Enterprise, whether or not considered causally is related. The

site investigator is responsible for informing their local IRB as per local requirements.

Investigators and other center personnel must inform appropriate Clinical Research Enterprise representatives via REDCap of any SAE that occurs in the course of the study within 1 day (i.e., immediately but no later than the end of the next business day) of when he or she becomes aware of it. Follow-up information on SAEs must also be reported by the Investigator within the same time frame.

An automated email alert will be sent to the designated Clinical Research Enterprise representative, when the page with SAE information is saved in REDCap by the Investigators or other site personnel. If REDCap is not available, then the Investigator or other study site personnel reports by fax an SAE to the appropriate Clinical Research Enterprise representative. A paper back- up SAE report is used for this purpose. The same reporting time frames still apply. The investigator is responsible for completing the eCRF as soon as the system becomes available again.

The Clinical Research Enterprise representative will work with the Investigator to compile all the necessary information and ensure that all the necessary information is provided to Vanderbilt University Medical Center within one calendar day of initial receipt for fatal and life-threatening events and within five calendar days of initial receipt for all other SAEs.

Reporting of serious adverse events to the FDA

The Sponsor will inform the regulatory authorities of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines.

Protocol Deviations

Investigators are required to adhere to the protocol, applicable federal (national) or state/local laws and regulations, and any conditions required by the IRB/Medical Ethics Committee (MEC), or applicable regulatory authorities.

A protocol deviation is used to describe situations in which the clinical protocol was not followed. All deviations from the protocol must be reported to Vanderbilt study staff per 21 CFR §812.150. In addition, all deviations must be reported to the reviewing IRB per the IRB's reporting requirements. The investigator shall state any mitigating circumstances or clinical reasoning that resulted in a protocol deviation. Examples of deviations would be required testing not done or an intervening medical condition preventing return for follow-up during the specified window.

The investigator must notify Vanderbilt study staff and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a patient in an emergency as soon as possible, but not later than 5 working days after the deviation has occurred, or no later than 5 working days after the investigator becomes aware of the deviation.

8.0 Monitoring of the study

During the study, a Clinical Research Enterprise representative will conduct regular monitoring visits with the study site. The monitoring visits may be conducted by phone, e-mail or by in-person visits to the study site. The monitoring visits will:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRF.
- Perform source data verification (a comparison of the data in the eCRF with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients.

The Clinical Research Enterprise representative will be available between visits if the investigator(s) or other study site personnel need information and advice about the study conduct.

9.0 Data Management

Data management will be performed by the Clinical Research Enterprise staff. Data will be entered into REDCap, a web-based data capture system at the study site. Trained site staff will be responsible for entering data on the observations, tests and assessments specified in the protocol into REDCap. Data entered in the REDCap will be saved to a central database and changes tracked to provide an audit trail. The data will then be source data verified, reviewed/queried and updated as needed. The Principal Investigator is responsible for electronically signing the eCRF. Data queries will be issued for inconsistent, improbable or missing data. All entries to the study database will be available in an audit trail. The data will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed, and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. A copy of the eCRF will be archived at the study site when the study has been locked.

Source data
The Clinical Trial Agreement (CTA) will specify the location of source data. Access to source documents and source data is essential to inspection and review of clinical studies by the Food and Drug Administration (FDA).

Recording of data
The REDCap Web-Based Data Capture system will be used for data collection and query handling. The site Principal Investigator will ensure that data are recorded in the electronic Case Report Forms (eCRF) and will ensure the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Trial Agreement.

Data will be entered in the eCRF by trained personnel using the REDCap system. When data have been entered, reviewed, edited, and source data verification has been performed, as appropriate, by a VUMC Clinical Research Enterprise representative, the data will be frozen to prevent further editing. The site Principal Investigator will be notified to sign the eCRF electronically. A copy of the eCRF data will be archived at the study site.

10.0 Study Withdrawal/Discontinuation

Participants may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

11.0 Statistical analysis

Statistical analysis will be performed using software STATA version 13 (StataCorp, College Station, TX). Baseline characteristics will be compared using Wilcoxon-Rank Sum test for continuous variables and Fisher's exact test for categorical variables. Multivariable regression analyses will be performed to assess for risk of primary and secondary outcomes with Lavare cycle on and off. Changes in laboratory parameters, echocardiographic measures, functional status and quality of life will be assessed using multivariable regression analyses. Statistical significance will be defined as $p<0.05$.

12.0 Privacy/Confidentiality Issues

All records and other information about subjects participating in the study will be treated as confidential.

The investigator agrees that the Sponsor (or Sponsor representative),

IRB, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

The investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations. Data generated by this trial will be considered confidential by the investigator.

Information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC); affiliated institution and employees, only under an appropriate understanding of confidentiality.

13.0 Follow-up and Record Retention

Duration of follow-up: 180-days; follow-up visits will be logged at 30-days, 90-days and 180-days.

FDA and ICH-GCP guidelines require that an Investigator retain subject identification codes, subject files, and source data for the maximum period of time permitted by the hospital, institution, or private practice, but not less than 2 years.

The investigator will follow the principles outlined in the Clinical Trial Agreement.