A silver lining in the VAD sky

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Impact of silver dressing on LVAD associated driveline infection

Objective

Driveline Infection remain a prevalent complication of LVAD therapy with rates varying between 10% and an astounding 50% depending on VAD centers report.[1,2,3] Driveline dressing protocols vary widely between centers and to date no randomized control trial (the gold standard for treatment evaluation) has been carried out.[4] Our aims are twofold:

- To evaluate the effectiveness of a silver-based driveline dressing protocol to reduce DLI as measured by DLI rate. Secondary goals measured will be DLI speciation, driveline site dermatitis rate, comfort, ease of use, protocol compliance and cost.
- To evaluate the feasibility of a multi-center RCT that would help establish a widely accepted consensus on driveline dressing practices

The physical and psychological burdens of driveline maintenance, driveline infection and allergic reactions to dressing kits components remain a major barrier to improved VAD patient's life expectancy and quality of life. No widely accepted protocols exist and no prospective randomized clinical trials to date have been carried out to evaluate a specific driveline dressing protocol.[4]

We posit that a silver-based dressing with weekly changes will reduce the rate of DLI and allergic reaction while improving patients' comfort and quality of life. Moreover, we hope that a prospective RCT, the gold standard for treatment evaluation, will catalyze the standardization of dressing change protocols across VAD centers. In this spirit we will broaden this single center trial to a multi-center trial to increase the significance and analytical power of the study.

Methods

This prospective research clinical trial will be conducted in a single academic medical center. The enrollment period is between January 1st, 2022 and December 31st, 2023. The initial follow-up period will be closed on December 31st 2023 with a continuation of the follow-up until December 31st 2024. Patients will be selected from current LVAD patients followed by our medical center clinic and from patients implanted with LVAD at our center during the study enrollment timeframe. Patients will be randomly assigned to the control protocol and the silver protocol. Both protocols will be taught to the patients and nursing staff by the VAD coordinators. The comparative evaluation will be done through adverse event collection, driveline culture results, patient survey and DL photos at specific intervals.

A. Inclusion Criteria

The following patients will be included in the study:

- >18 years of age
- Implanted with LVAD as DT or BTT at the Academic Medical Center with implantation scheduled between January 1st, 2022 and December 31st, 2023
- Implanted prior to January 1st 2022 with no history or signs and symptoms of DLI as of January 1st 2022.

B. Exclusion criteria

The following will be excluded from the study. Patients with

- A history of DLI
- A history of sternal wound infection
- Implantation secondary to VAD exchange for device infection

C. Interventions

A new driveline dressing kit will be trialed on patients randomized to the intervention arm of the study. Both arms will have a regular dressing kit and a sensitive dressing kit.

The trial arm kits include:

a. For standard dressing: a silverlon antimicrobial patch, CHG swabs for cleaning, an occlusive dressing with window, and driveline anchors. The driveline dressing change frequency will be weekly.
b. For sensitive skin dressing: a silverlon antimicrobial patch, Providone/iodine swabs for cleaning, an occlusive dressing with window, and sensitive driveline anchors. The driveline dressing change frequency will be weekly.

The control arm kits include:

a. For standard dressing: No antimicrobial barrier, CHG swabs for cleaning, an occlusive dressing with window, and driveline anchors. The driveline dressing change frequency will be every 96 hours.
b. For sensitive skin dressing: No antimicrobial barrier, Providone/iodine swabs for cleaning, an occlusive dressing with window, and driveline anchors. The driveline dressing change frequency will be every 96hr.

D. Assessment

The following endpoints will be assessed for patients in both arms of the study enrolled between 01/01/2022 and 12/31/2023 and comparison will be drawn between the 2 groups:

1. DLI rate in number per 100-patient month
2. Time to first DLI in days

E. Data Management

Data is collected by the PI and analyzed by our data analyst. Additionally, cost data will be collected via our purchasing analyst who will retain data on number ok kits sent to each patient. Patients will be deidentified for all data collection. Data is stored behind the medical center firewall and encryption software. Data is accessible to the PI, the data analyst and our medical director.

F. Statistical Analysis Plan (SAP)

Study Design:

A randomized controlled trial (RCT) in which patients are randomly assigned to one of two groups:

a. Silver Dressing Group
b. Standard Dressing Group

Primary Outcome:

- Rate of driveline infection in number per 100 patient month, defined as number of driveline cultures positive for bacterial infection per 100 months of patients on support.

Secondary Outcome(s):

- Mean time to first driveline infection, defined as a number of days to first positive culture.

Covariates to Control for:

- Body Mass Index (BMI)
- Gender

- INTERMACS Level

Statistical Analysis Overview:

The analysis will focus on univariate tests to assess the differences between silver dressing and standard dressing groups, while controlling for covariates such as BMI, gender, and INTERMACS level. The significance level for all analyses will be set at $p < 0.05$.

Data Cleaning and Assumptions:

- Missing data will be addressed using appropriate techniques, such as multiple imputation or complete case analysis, depending on the nature and extent of missing data.
- Assumptions of normality will be assessed for continuous variables, and non-parametric tests will be considered for non-normally distributed data.

Univariate Analysis:

- For continuous outcomes, descriptive statistics (mean, standard deviation) will be presented for each treatment group. Between-group comparisons will be made using a two-sample t-test (if data are normally distributed) or a Mann-Whitney U test (if data are non-normally distributed).
- For categorical outcomes, descriptive statistics (frequencies and percentages) will be presented for each group. Between-group comparisons will be conducted using the chi-square test or Fisher's exact test, as appropriate.
- Univariate analysis will focus on comparing the primary and secondary outcomes between the two treatment groups, without adjusting for covariates.

Multivariate Analysis (Controlling for Covariates):

- Linear regression will be used to compare the treatment effects while adjusting for BMI, gender, and INTERMACS level. These covariates will be included as fixed effects in the model.
- The significance level for all covariates will be set at $p < 0.05$ in the final model, following a backward elimination procedure, if necessary, to identify the most relevant covariates.

Model Assumptions and Diagnostics:

- The assumptions for each regression model will be checked. For linear regression, normality of residuals, linearity, and homoscedasticity will be assessed.

Sensitivity Analyses:

- Sensitivity analyses will be conducted to evaluate the robustness of the results by varying handling strategies for missing data and by testing the impact of potential outliers.

Statistical Software:

- All analyses will be conducted using SAS version 9.4.

Data Handling and Quality Assurance

- Data is collected by the PI and analyzed by our data analyst. Patients are deidentified for all data collection. Data is stored behind the medical center firewall and encryption software. Data is accessible to the PI, the data analyst and our medical director.
- Outliers and implausible values will be reviewed and resolved.

Reporting

- Results will be reported in accordance with CONSORT guidelines.
- Findings will be disseminated through peer-reviewed publications and conference presentations.

Conclusion:

The statistical analysis will provide insight into the comparative effectiveness of silver dressing versus standard dressings while controlling for potential confounders such as BMI, gender, and INTERMACS level. The univariate analysis will provide preliminary insights into dressing effect,

with multivariate models ensuring a more rigorous adjustment for confounding variables. All analyses will be conducted at a significance level of $p < 0.05$.

References

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CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A silver lining in the VAD sky?
Impact of silver dressing on LVAD associated driveline infection

This is a medical research study. Your study doctor, Dr. Liviu Klein, and the research team from the UCSF Department of Cardiology will explain this study to you.

Medical research studies include only people who choose to take part. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor.

You are being asked to take part in this study because you will receive a Left Ventricular Assist Device (LVAD) to help your heart pumping and supplying blood to the rest of your body. The LVAD is connected through a driveline (a tube containing electrical leads connected to the device in your body) that passes through the skin and is connected to a power supply outside your body. The driveline insertion site is a potential entry point for bacteria and needs to have a dressing placed in a sterile fashion on it to prevent infection.

Why is this study being done?

The purpose of this study is to evaluate the safety and effectiveness of a new driveline dressing kit that contains a silver patch (the "Silverlon" dressing kit) compared to our current dressing kit that does not contain a silver patch. Both kits contain anchors that help secure the driveline and are standard of care. The silver patch has been used in other VAD centers and on central line dressing kits.

To ensure that outcomes from the study are evaluated in a fair manner, the protocol requires that patients be randomized to either the dressing kit with no silver patch or the dressing kit with the silver patch. Randomization is a process by which patients are assigned to receive either the Silverlon driveline dressing kit (the "treatment group"), or the standard driveline dressing kit (the "control group") with no advance knowledge by either the patient or physician. The randomization process is designed so equal numbers of patients receive the treatment driveline dressing kit (Silverlon kit) or one of the control group devices (standard kit). Patients will receive the same care and follow-up regardless of which driveline dressing kit is used.

The randomization process ensures that you have a 50-50 chance of receiving either the Silverlon driveline dressing kit or the standard dressing kit.

New Driveline Dressing Kit Description
The Silverlon patch is a small silver-plated patch designed to help prevent infection of central catheters. Silver is a long-known antimicrobial. The Silverlon patch contains a high amount of metallic silver. When activated by moisture, the patch releases Silver ions that are effective against a wide spectrum of wound pathogens.

Although we do not currently use the Silverlon Dressing kit, it has been used at other VAD centers and is approved for use by the FDA to prevent infections in central catheters. The Silverlon dressing kit is also approved by the FDA for safety. The results of this study may be used to support marketing of the patch in the future.

Financial Statement
Silverlon, Inc. is not providing any funding to Doctor Liviu Klein, Doctor Georg Wieselthaler or UCSF to do this study.
Dr. Liviu Klein and Dr. Geor Wieselthaler are not receiving any funding from Silverlon for participating this study. They have no financial interest in Silverlon Inc., including stocks or stock options. Additionally, they do not receive money for activities such as speaking or consultations, honoraria, grants to fund ongoing research or compensation in the form of equipment or supplies.

How many people will take part in this study?
About 20 subjects will be enrolled for this study at this site. This study is a pilot that may be expanded to a multicenter trial.

What will happen if I take part in this research study?

During the screening for study eligibility.

You will have tests performed before your VAD is implanted, including a medical history and physical exam, checks of your heart rate and blood pressure, measurement of your urine output, a record of your medications, and blood tests. These tests will help your doctor decide if you are a candidate for the VAD. If you are not a suitable candidate to receive a VAD, you will not participate in the study, and you will not undergo randomization and treatment as defined by this clinical trial. However, your doctor will discuss all other treatment options with you.

You will need to have the following "screening" exam to find out if you are eligible to be in the study before you receive your VAD pump. We estimate that the screening exam will take up about 10 minutes of your time in total. The screening exam will consist of:

- **Medical chart review:** Your medical chart will be reviewed by the study doctors.

- **Health history**: You will be asked questions about your overall health, allergies you may have, other conditions you may have, prior surgeries, and medications you may be taking for these conditions, including those prescribed by your doctor and over-the-counter medications. You will be asked about known sensitivity to silver or nylon. You will also be asked if you have previously or are now taking part in any other studies.

During the Implant Procedure...

If the screening review shows that you are eligible to be in the study, and you choose to take part, then you will have the following procedure done:

The implantation of the LVAD will be according to the standard of care and will require a major operation, using an incision over your sternum (breastbone) and/or your ribs. As in other types of heart surgery, it will be necessary to use a heart-lung machine to support your blood flow during implantation of the LVAD. The driveline will be threaded through your chest and connected to the VAD controller to start the VAD pump. Once the surgery is completed and before leaving the operating room, your VAD coordinator will take a picture of the driveline insertion site and place it in your chart. Your VAD coordinator will then place either the standard dressing or the Silverlon dressing on your driveline insertion site using the standard or the Silverlon Dressing kit in a sterile fashion.

The placement of the Silverlon dressing will take about 5 minutes. It is the same amount of time as the standard driveline dressing protocol.

When you are finished receiving the LVAD implantation and before you leave the hospital

While recovering from the implant surgery, you will stay in the hospital, your driveline will be changed and dressed every 7 days by your VAD coordinators using the standard or the Silverlon dressing Kit and following either the standard or the Silverlon dressing change protocol. During this period, you will be routinely monitored to make sure there are no signs and symptoms of infection at your driveline site. We will also take pictures of the driveline site, removing any potential patient identifiers on the picture. The following is a list of information that will be tested as part of routine care and collected for throughout your hospital stay.

Daily

- Serum labs, including CBC, procalcitonin, CRP
- Driveline site assessment
- Driveline integrity assessment
- Device parameters
- Any adverse events

Training

You and your caregivers will receive training from your VAD coordinator on sterile driveline dressing change using the standard or the Silverlon dressing kit. You will practice on a mannequin and, after demonstrating competency, your caregiver will perform the driveline dressing change on you (the patient) under supervision by the VAD coordinator

After you leave the hospital

Per our standard of care, your VAD coordinator will call you at least weekly to inquire on your

well being. The following information may be collected during call follow-up:

- Driveline self-assessment
- Device parameters
- Any adverse events
- Medications review

The following information will be collected during the in clinic follow-up visits and are part of routine care:

- Physical exam
- Driveline site exam
- Driveline pictures
- Driveline site cultures
- Serum labs including CBC
- Device parameters
- Any adverse events
- Medications review

As part of the study you will be asked to complete questionnaires at 1 month, 3 month, 6 month and 12 month. These questionnaires are designed to gather feedback on your experience with the dressing kits. We estimate that filling out these questionnaires will take approximately 5 minutes

Study location: All these procedures will be done during your hospital stay (505 Parnassus Avenue) or in the Heart Failure / Transplant clinic (400 Parnassus Avenue).

How long will I be in the study?

Participation in the study begins when the VAD pump is implanted and ends at 2 year or when a patient receives a donor heart or when the VAD pump is removed due to heart recovery, or at death, whichever comes first.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop your participation safely.

This research project may stop for a variety of reasons. These may include reasons such as unacceptable side effects, the dressing kit being shown not to be effective, or further investigation not needed.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects you experience while taking part in the study. The risks associated with the Driveline Dressing Kit may increase the longer you are using the kit. These risks are described below.

Several risks are associated with participating in this study. Your study doctor will discuss them with you. The risks may include:

Risks:

Rare (less than 10%)

- Allergy to components of the patch: Silver and/or nylon
- Infection

Randomization risks: You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

- **Blood drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick, bruising, infection, and fainting.

- **Reproductive risks:** If you are pregnant or plan to become pregnant or are nursing a baby, you cannot enter this study. There may be a risk of severe problems to you or your unborn baby. Women may participate in this study only if they are past menopause, have had surgery to make them sterile, or are using an acceptable form of birth control throughout the course of the study. If you become pregnant during the trial, you must notify your doctor immediately. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

Unknown Risks: The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.
For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

If you are in the group that receives the Silverlon driveline dressing Kit and it proves to be superior to standard therapy, you may benefit from participating in the study, but this cannot be guaranteed. The study device will be considered a success if outcomes are equivalent to, or better than, current commercial kits, within an acceptable margin of error.
As explained to you, other potential indirect benefits are possible also, including the gathering of information regarding the optimal driveline dressing kit system for VAD patients.

What other choices do I have if I do not take part in this study? Your other choices may include:

- Getting standard treatment without being in a study.
- Getting a different experimental treatment/taking part in another study.

How will information about me be kept confidential?

Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. If you do not have a UCSF medical record, one will be created for you. Your signed consent form and some of your research tests will be added to your UCSF medical record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Study tests that are performed by research labs and information gathered directly from you by the researchers will be part of your research records but will not be added to your medical record. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy and share your medical records for research, quality assurance, and data analysis include:

- The University of California

- The Food and Drug Administration (FDA), the Data and Safety Monitoring Board (DSMB)members, Clinical Events Committee (CEC) members and other U.S. and foreign government agencies involved in keeping research safe for people.

What are the costs of taking part in this study?

Two types of procedures will be done during this study. Some are part of your standard medical care and others are only for research. You or your insurer will be billed for the standard medical care. You will be responsible for your co-pays, deductibles, and any other charges that your insurer will not pay. There is a possibility that your insurer may not cover all standard medical care costs if you are receiving medical services out of network. Any procedures done only for research will not be charged to you or your insurer.

Will I be paid for taking part in this study?

You will not be paid or offered any other compensation for taking part in this study.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at (415) 514-5823.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs or covered by the University of California depending on a number of factors. The University does not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Committee on Human Research at (415) 476-1814.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution. Your participation in the study may be stopped at any time by your doctor without your consent. If you withdraw or are withdrawn from the study for any reason, you may be asked to return to the clinic for a follow-up examination.

This research project may stop for a variety of reasons. These may include reasons such as unacceptable side effects, the dressing kit being shown not to be effective or further investigation not needed.

During the study, new information about the risks and benefits of the Silverlon dressing kit may become known to researchers and might alter your willingness to continue your participation in the study. If this occurs, we will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study**.** This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions, concerns, or complaints you have about this study. Contact your study doctor Dr. Liviu Klein at telephone number (415) 502-8584 or 415-514-5823

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may haveabout the study, please call the Office of the Committee on Human Research at (415)476-1814.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT

You have been given signed and dated copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

You have been given time to read this consent and the study has been explained to me and all my questions relating to the study device and procedures have been answered to my satisfaction.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

Date	Participant's Signature for Consent
Date	Person Obtaining Consent
Date	Witness – Only required if the participant is a non-English speaker