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**Destination LVAD as therapy for patients with end stage heart failure and severe pulmonary hypertension**

**Study Purpose and Rationale**

Orthotopic heart transplant (OHT) is the most effective therapeutic option for patients with end-stage heart failure. However, the donor pool is limited and as such, patient selection is critical. The condition of patients with end-stage heart failure is often worsened by concomitant pulmonary hypertension due to chronic fluid overload as evidenced by consistently elevated wedge pressure. One of the most important components of the OHT evaluation is the assessment of the pulmonary circulation and right ventricular function, as preoperative pulmonary vascular resistance (PVR) is a known independent risk factor for death after OHT[1], and risk factor dysfunction accounts for approximately 50% of cardiac complications and 20% of early mortality[2]. It has been established that for patients who are otherwise candidates for OHT but who have elevated PVR refractory to medical therapy, left ventricular assist device (LVAD) implantation can serve as an effective means of lowing the PVR and bridging the patient to transplant[3]. However, oftentimes patients with end-stage HF often are not candidates for OHT for a variety of reasons including age, social support, and comorbid conditions. These patients often have concomitant pulmonary hypertension due to long-standing heart failure. Their quality of life and life expectancy are limited by symptoms of both advanced heart failure and pulmonary hypertension. Although the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial showed LVAD as destination therapy for patients with NYHA Class IV heart failure to be an effective means of improving quality of life and survival[4], the trial did not include patients with advanced pulmonary hypertension, and inotrope-dependence was not a requirement for inclusion[5]. The INTrEPID (Investigation of Nontransplant-Eligible Patients Who Are Inotrope Dependent) trial[6] was an observational study that attempted to determine if end-stage heart failure patients with severe pulmonary hypertension would benefit from LVAD placement by comparing LVAD and medical therapy in patients who were inotrope-dependent. Although this study found that there was a trend towards improved survival in the LVAD group, the patients in the study were allowed to choose their own study arm; there was no randomization. Also, the INTrEPID study did not specifically examine patients who had advanced pulmonary hypertension. It remains unknown whether LVAD as destination therapy in those patients with end-stage heart failure and advanced pulmonary hypertension would be beneficial.

An elevated PVR and an increased transpulmonary gradient may be responsive to and reversible with vasodilating agents, or it may be fixed due to fibrosis and remodeling[7]. Right heart catheterization and measurement of hemodynamic parameters with and without intravenous vasodilators are necessary to discriminate between medically reversible and irreversible pulmonary hypertension. This study aims to determine if LVAD as destination therapy in patients with both end-stage heart failure and severe medically refractory pulmonary hypertension improves quality of life and/or survival. We propose a randomized, non-blinded clinical trial to compare LVAD versus optimal medical therapy in patients with end stage heart

failure and severe pulmonary hypertension who are not candidates for orthotopic heart transplant.

**Study Design and Statistical Analysis**

This study will include patients with NYHA Class IV heart failure and severe pulmonary hypertension who are not candidates for OHT. Using a stratified randomization to ensure similar baseline characteristics of the two groups, the study participants will be divided into optimal medical therapy (OMT) and LVAD therapy. OMT will be defined by the medical committee with the goal of optimizing organ perfusion and minimizing symptoms; therapy with inotropes will not be discouraged. We will use the Incor LVAD (BerlinHeart AG, Berlin, Germinany) based on past experience with the device[8]. There will be two primary endpoints: early (6-month) survival and late (12-month) survival. We will also score the patients on the Minnesota Living with Heart Failure questionnaire prior to randomization in order to include the scores on each test in the stratified randomization. The patients will also be scored at the prespecified time points of 1 month after randomization, 2 months after randomization, 3 months after randomization, 6 months after randomization, and at 12 moths after randomization.

A power calculation has been done using the unpaired t-test, and we have determined that at least 60 study participants will be needed; the goal is to enroll a total of 100 participants over a 24 month period. Assuming 80% power for a p value of 0.05:

$$n \text{ (in each group)} = 1 + 16 (SD/effect)^2$$

SD is of outcome measure across subjects and is assumed to be 36 weeks. The effect is the postulated group difference in outcome measure and was assumed to be 24 weeks. Although the REMATCH trial saw a difference in median survival of 36 weeks[9], we postulate that the partipants in this study will be overall more critically ill due to their known severe pulmonary hypertension and will therefore benefit less from LVAD placement.

$$n = 1 + 16 (36/24)^2$$
$$n = 36$$

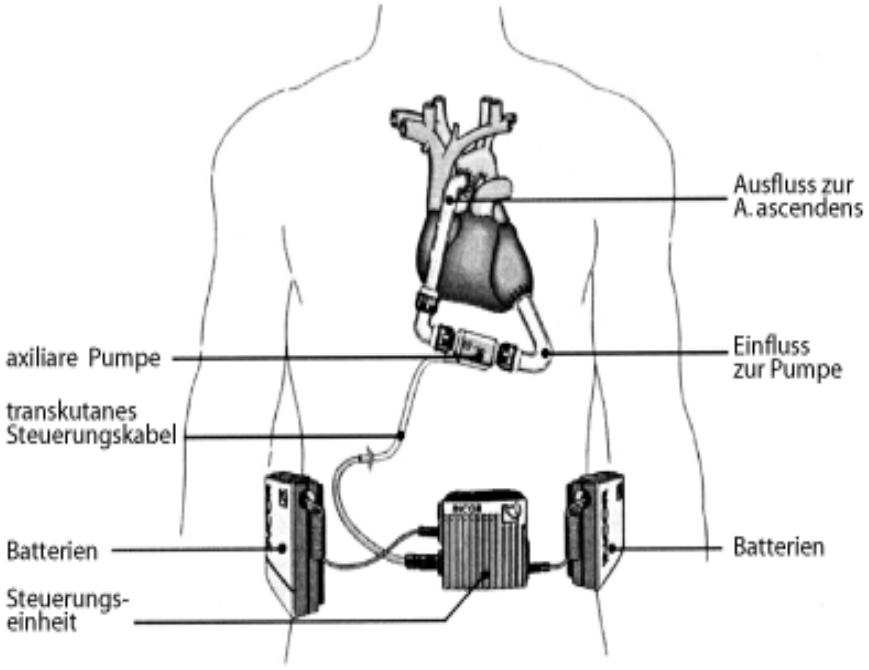
We expect that the study participants will not cross over from one group to another and all statistical analysis will be done on an intention to treat basis using a t-test for survival time as well as a chi-squared test for 6 month versus 12 month mortality. Given there is the potential for the device to increase mortality, all statistical tests will be two-tailed. We expect to randomize 5 patients per month; the initial enrollment should be complete by 24 months. The study will continue for a total of 36 months after the date of enrollment of the last patient.

**Study Procedure**

All patients with NYHA Class IV Heart Failure and known pulmonary hypertension with PVR (pulmonary vascular resistance) >/= 6 Woods Units that is unresponsive to pharmacologic intervention with a contraindication to orthotopic heart transplant as defined by their primary cardiologist will be offered enrollment in the study. Patients who would be candidates if not for an elevated PVR will not be enrolled, and will be offered LVAD as bridge to transplant. At baseline, all patients will be required to undergo routine blood tests, transthoracic

echocardiogram, and right heart catheterization (routine in patients being considered or excluded for OHT), as well as complete the Minnesota Living with Heart Failure Questionnaire in order to establish baseline characteristics. Other baseline information will be gathered from the medical record as needed, with the consent of the patient. All patients will undergo routine pre-surgical evaluation, and those patients who are not deemed candidates for surgery will be excluded from the study. This will include patients who will be unable to have the LVAD implanted for pre-specified reasons including contraindication to anticoagulation, history of OHT, LV reduction procedures, or cardiomyoplasty, presence of an implanted mechanical aortic valve, evidence of untreated abdominal aortic aneurysm >5cm. After this data is collected, the patients will undergo stratified randomization to either the optimum medical treatment group or the LVAD group. The participants will be evaluated regularly by their primary physicians as well as monthly for 3 months and then every 3 months by the study investigators. As stated earlier, we expect the quality of life questionnaires to be evaluated at the pre-specified time points of 1 month after randomization, 2 months after randomization, 3 months after randomization, 6 months after randomization, and at 12 months after randomization.

**Medical Device: INCOR LVAD**
The INCOR LVAD is diagramed below.




The Incor LVAD is a commercially available device manufactured by Berlin Heart AG, in Germany. It is an implantable, magnetically accentuated axial flow pump that delivers non-pulsatile flow designed to support the left ventricle for extended periods of time. It is small, weight only about 200 grams, and easily implantable in the pericardium. The system also consists of an external control unit and two rechargeable batteries, which allow the patient nearly unlimited mobility. A laptop starts, controls, and adjusts the pump. A power supply and a charging unit are also included.

Previous studies have been done using the Incor LVAD. In 2005, a German group published the first clinical experience with the Incor LVAD, and found it comparable to other LVAD devices with no difference in adverse event rates[10]. In 2008 an Italian group compared the Incor LVAD with pulsatile-flow devices and found them to be comparable[11]. The Incor has also been used in an observational study comparing LVAD with medical therapy in patients with severe pulmonary hypertension as a bridge to heart transplant[12]. The Incor LVAD is considered safe and effective.

**Study Questionnaires**

We will use the Minnesota Living With Heart Failure Questionnaire. This questionnaire was also used in the REMATCH trial, and is shown on the following page.

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

| **Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -** | **No** | | | **Very Little** | | **Very Much** |
|---|---|---|---|---|---|---|
| 1. causing swelling in your ankles or legs? | 0 | 1 | 2 | 3 | 4 | 5 |
| 2. making you sit or lie down to rest during the day? | 0 | 1 | 2 | 3 | 4 | 5 |
| 3. making your walking about or climbing stairs difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 4. making your working around the house or yard difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 5. making your going places away from home difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 6. making your sleeping well at night difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 7. making your relating to or doing things with your friends or family difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 8. making your working to earn a living difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 9. making your recreational pastimes, sports or hobbies difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 10. making your sexual activities difficult? | 0 | 1 | 2 | 3 | 4 | 5 |
| 11. making you eat less of the foods you like? | 0 | 1 | 2 | 3 | 4 | 5 |
| 12. making you short of breath? | 0 | 1 | 2 | 3 | 4 | 5 |
| 13. making you tired, fatigued, or low on energy? | 0 | 1 | 2 | 3 | 4 | 5 |
| 14. making you stay in a hospital? | 0 | 1 | 2 | 3 | 4 | 5 |
| 15. costing you money for medical care? | 0 | 1 | 2 | 3 | 4 | 5 |
| 16. giving you side effects from treatments? | 0 | 1 | 2 | 3 | 4 | 5 |
| 17. making you feel you are a burden to your family or friends? | 0 | 1 | 2 | 3 | 4 | 5 |
| 18. making you feel a loss of self-control in your life? | 0 | 1 | 2 | 3 | 4 | 5 |
| 19. making you worry? | 0 | 1 | 2 | 3 | 4 | 5 |
| 20. making it difficult for you to concentrate or remember things? | 0 | 1 | 2 | 3 | 4 | 5 |
| 21. making you feel depressed? | 0 | 1 | 2 | 3 | 4 | 5 |

**Study Subjects**

Inclusion criteria will include:

- NYHA Class IV heart failure for at least 90 days prior to randomization
- Age greater than 18 years at time of enrollment
- Negative pregnancy test
- Ineligibility for heart transplant for one or more of the following reasons:
  - Age greater than 65years
  - Presence of insulin-dependent diabetes mellitus with evidence of end-organ damage
  - Chronic renal failure with documentation of a sustained serum creatinine level greater than 2.5mg/dL for 90 days prior to randomization
  - Any major cormorbidity (physical or psychiatric) that would make the patient ineligible for cardiac transplantation
- Maximal oxygen consumption of 12mL/kg/min or less or have been resistant to weaning from intravenous inotropic therapy
- Current medication regimen including beta-blocker (if tolerated), digoxin, diuretics, and an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 90 days prior to randomization
- Left ventricular ejection fraction (LVEF) <25% seen via left heart catheterization or transthoracic echocardiogram despite medical therapy for at least 90 days prior to randomization
- Pulmonary vascular resistance (PVR) >6 Woods Units, not reversible with medical therapy, for at least 30 days prior to randomization

Exclusion criteria will include:

- Age less than 18 years at time of enrollment
- Cause of heart failure due to uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, or active myocarditis
- International normalized ratio >1.3 or prothrombin time >15s within 24h before randomization
- Body surface area < $1.5m^2$
- Body mass index > $40kg/m^2$
- Positive serum pregnancy test
- Severe chronic obstructive pulmonary disease with forced expiratory volume </= 1.5L/min
- History of prior cardiac transplantation, left ventricular reduction procedure, or cardiomyoplasty
- Presence of an implanted mechanical aortic valve that is unable to be converted to bioprosthesis at the time of LVAD implantation
- Evidence of intrinsic hepatic disease or biopsy-proven cirrhosis
- Cerebrovascular accident within 90 days of randomization or history of >80% carotid stenosis by Doppler
- Presence of Alzheimer's disease or other irreversible dementia
- Untreated abdominal aortic aneurysms >/= 5cm measured via abdominal ultrasound within 30 days of randomization

- Active or suspected systemic infection
- Platelet count <50,000/$mm^3$
- Serum creatinine >/= 3.5mg/dL or need for dialysis
- Participation in another study

**Recruitment of Subjects**
Potential subjects will be recruited from this institution, New York-Presbyterian Columbia Medical Center by disseminating information regarding the study to all practicing cardiologists and internists. The study will enroll patients who are referred to the study investigators by their regular physicians.

**Confidentiality of Study Data**
All study participants will be given a unique identifier; data will be stored in a secure location that is accessible only to the study investigators. Participants will be required to release their medical information to the study investigators. No blood or tissue will be stored for further investigation.

**Potential Conflict of Interest**
We report none as the study investigator has no ties to industry and no financial stake in any biomedical devices or Berlin Heart, the maker of the Incor LVAD.

**Location of Study**
The study will be conducted at CPMC, including the surgical operating rooms, the cardiac care unit, the cardiothoracic intensive care unit, and the clinical laboratories of the department of cardiology.

**Potential Risks**
Potential risk include the risk of death, stroke, bleeding, infection, and permanent disability during, immediately after, and long-term after LVAD placement. The risks for optimal medical treatment also include death, stroke, bleeding, catheter infection, or permanent disability. It is possible that the LVAD placement will hasten death, or that the risk of implantation outweighs any benefit of LVAD placement.

**Potential Benefits**
Potential benefits include improved quality of life or survival with the LVAD placement. There is the possibility that the subjects will not benefit as a result of participation in the study.

**Compensation to Subjects**
The patients will be compensated $100.00 each time they complete the study questionnaire.

**Costs to Subjects**
There is no cost to the subject participants. All hospitalization, surgical, and medical costs will be paid for by the patient's insurance or will be paid for by the study itself. If the subject cannot arrange transportation for follow-up, it will be provided free of charge.

**Minors as Research Subjects**

This study excludes all minors as well as those incapable of making their own medical decisions.

**Radiation or Radioactive substances**
There is no known exposure to radiation or radioactive substances in this study.

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