

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Miller LW, Pagani FD, Russell SD, et al. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007;357:885-96.

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Electronic Supplementary Appendix: Study Enrollment Criteria, Anticoagulation Regimen, and Adverse Event Definitions

Inclusion Criteria

1. Patient or their legal representative has signed an informed consent.
2. Transplant listed.
3. Body Surface Area (BSA) $\geq 1.2 \text{ m}^2$.
4. New York Heart Association class IV heart failure symptoms.
5. Female patients of childbearing potential must agree to use adequate contraceptive precautions (defined as oral contraceptives, intrauterine devices, surgical contraceptives or a combination of condom and spermicide) for the duration of the study.
6. On inotropic support, if tolerated.
7. Despite medical therapy, the patient must meet one of the following criteria:
 - a. No contraindication for listing as Status 1A **or**;
 - b. No contraindication for listing as Status 1B and meet the following hemodynamic criteria (collected within 48 hours of enrollment):
 - PCWP or PAD $\geq 20 \text{ mmHg}$, and
 - Cardiac Index $\leq 2.2 \text{ L/min/m}^2$ or systolic blood pressure $\leq 90 \text{ mmHg}$

Exclusion Criteria

Patients will be excluded from study participation for any one or more of the following:

1. Etiology of heart failure due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis or restrictive cardiomyopathy.
2. Technical obstacles, which pose an inordinately high surgical risk, in the judgment of the investigator.
3. Existence of any ongoing mechanical circulatory support other than intra-aortic balloon counterpulsation.
4. Body Mass Index (BMI) $> 40 \text{ kg/m}^2$.
5. Positive pregnancy test if of childbearing potential.
6. Presence of mechanical aortic cardiac valve that will not be converted to a bioprosthesis at the time of LVAD implant.
7. History of cardiac transplant.
8. Platelet count $\leq 50,000/\text{ml}$.
9. Evidence of an untreated aortic aneurysm $\geq 5\text{cm}$.

10. Psychiatric disease, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAD management.
11. Presence of an active uncontrolled infection.
12. Intolerance to anticoagulant or antiplatelet therapies or any other peri/post operative therapy the Investigator will require based upon the patient's health status.
13. Presence of any one of the following risk factors for and indicators of severe end-organ dysfunction or failure:
 - a) An INR ≥ 2.5 which is not due to anticoagulant therapy or Plavix administration within 5 days.
 - b) A total bilirubin that is $> 5\text{mg/dl}$, or shock liver (e.g. transaminases $> 2,000$), or biopsy proven liver cirrhosis.
 - c) History of severe COPD or severe restrictive lung disease.
 - d) Fixed pulmonary hypertension, with a most recent PVR > 6 Wood units, that is unresponsive to pharmacological intervention.
 - e) History of unresolved stroke or uncorrectable cerebrovascular disease.
 - f) Serum creatinine $\geq 3.5\text{ mg/dl}$ or the need for chronic renal replacement therapy (e.g. chronic dialysis).
 - g) Significant peripheral vascular disease accompanied by rest pain or extremity ulceration

14. The patient has moderate to severe aortic insufficiency without plans for correction during pump implantation surgery.
15. Participation in any other clinical investigation that is likely to confound study results or affect study outcome.

Anticoagulation Regimen

The following anticoagulation regimen as a guideline was agreed upon by study investigators and used for this study: 1) initiation of an intravenous infusion of unfractionated heparin 12 to 24 hours following implantation or when thorocostomy tube drainage is < 50 ml/hour; 2) titration of the heparin infusion to a partial thromboplastin time (PTT) of 45-50 seconds for 24 hours following implantation; 3) after 24 hours titration of the heparin infusion to a PTT goal of 50 to 60 seconds; 4) after an additional 24 hours titrate the heparin infusion to a PTT goal of 55 to 65 seconds; 5) initiation of antiplatelet therapy on postoperative day 2 to 3 with aspirin 81 mg daily and dipyridamole 75 mg three times daily; 6) on postoperative day 3 to 5 and following removal of thorocostomy tubes, initiate anticoagulation with warfarin titrating the dose to an international normalized ratio (INR) of 2 to 3 and discontinue heparin after obtaining a therapeutic INR.

Adverse Event Definitions

Neurologic Event:

Any new, temporary or permanent, focal or global neurological deficit including TIA, metabolic encephalopathy, seizure, etc. The event must be sub-categorized to document the type of neurologic event.

Stroke:

A stroke is a neurological deficit lasting more than 24 hours, or lasting 24 hours or less with a brain imaging study showing new infarction. A TIA is a neurological deficit lasting less than 24 hours and, if an imaging study is performed, shows no evidence of new infarction. Each stroke must be subcategorized as either ischemic or hemorrhagic. The NIH Stroke Scale and Modified Rankin Scale require completion at the time of Stroke (The NIH Stroke scale must be completed by a Neurologist). The NIH Stroke Scale must be re-administered by a Neurologist at 30 and 60 days following the event to document the presence of neurological deficits. The Modified Rankin Scale is also required at 30 and 60 days following the event.

Bleeding:

An episode of internal or external bleeding that causes death, re-operation, permanent injury, or necessitates transfusion of ≥ 2 units of red blood cells within 24 hours.

Hemorrhagic stroke should be classified as a neurologic event and not as a separate bleeding event.

Localized Infection:

Infection localized to any organ system or region without evidence of systemic involvement which requires treatment or is ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal and protozoal infection, by standard clinical pathologic/laboratory methods. This definition includes positive blood cultures that are not considered to be septic in etiology.

Percutaneous Site Infection:

Infection of the percutaneous drive line site evidenced by the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, and or leukocytosis. This definition includes any positive cultures identified at the time of pump explant.

Pump Pocket Infection:

Infection of the pump pocket area evidenced by the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, and or leukocytosis. This definition includes any positive cultures identified at the time of pump explant.

Pump Housing, Inflow or Outflow Tract Infection:

Infection of blood-path surfaces or intra-corporeal components of the LVAD documented by positive site culture.

Sepsis:

A systemic response to a serious infection, usually manifested by fever, tachycardia, tachypnea, leukocytosis and vasodilatation requiring use of IV antimicrobial therapy. It may or may not be associated with a localized site of infection. It may or may not be accompanied by a positive microbiological culture from the blood, the localized site of infection or other evidence of bacterial, viral, fungal, or protozoal infection using standard clinical pathologic/laboratory methods. This definition excludes routine prophylactic treatment with IV antimicrobial therapy.

Peripheral (Non-CNS) Thromboembolic (TE) Event:

Any thrombus or thrombo-embolism in the pulmonary or systemic circulations confirmed by: 1) standard clinical and laboratory testing, or 2) operative findings, or 3) autopsy findings, or 4) that requires empirical intervention. This definition excludes neurological events.

Device Thrombosis:

Any obstructive thrombus in the device or its conduits associated with clinical symptoms of impaired pump performance (e.g. decreased pump flow, need to increase pump speed, increased power, hemolysis) or the need for thrombolytic or surgical intervention. In addition, pumps will be analyzed at Thoratec. Any severe thrombus scored as a level 3 thrombus (>50% obstruction) will be captured as an event.

Cardiac Arrhythmias:

Any symptomatic or asymptomatic arrhythmia that requires intervention. The investigator should distinguish four types of events: 1) cardiac arrest, 2)ventricular arrhythmia, 3) supraventricular arrhythmia, 4)atrial arrhythmia.

Myocardial Infarction:

The presence of at least two of the following three criteria: a) a clinical history of ischemic-type chest discomfort, 2) changes on serially obtained electrocardiographic tracings, 3) a rise and fall in serum cardiac markers. Myocardial infarcts that occur within 7 days of implant will be classified as peri-operative events.

Respiratory Failure:

Impairment of respiratory function requiring reintubation and/or tracheostomy at any time **or** the inability to discontinue ventilatory support after six days (144 hours) of VAD support.

Renal Failure:

Abnormal kidney function requiring dialysis (including hemofiltration and CVVH) in patients who did not require this procedure prior to implant.

Chronic Renal Dysfunction:

An increase in serum creatinine of 2 mg/dl above baseline sustained for at least 90 days.

Hepatic Dysfunction:

Liver function studies that are greater than three times the baseline values in any two of the three liver function studies (total bilirubin, AST and ALT), measured by standard clinical pathology/laboratory medicine methods, sustained for 14 days (or if hepatic dysfunction is the primary cause of death).

Psychiatric Episode:

Disturbance in thinking, emotion or behavior that causes substantial impairment in functioning or marked subjective distress requiring intervention.

Right Heart Failure:

Symptoms of right heart failure (e.g. drop in right ventricular ejection associated with right sided congestion including hepatic congestion, peripheral edema, jugular venous distension, etc.) requiring either RVAD implantation at any time, or inotropic therapy ≥ 14 days following implant.

Hemolysis:

Two consecutive plasma-free hemoglobin (PFHgb) values greater than 40 mg/dl within 24-hours of each other and an LDH value greater than 1,000 mg/dl within the same 24-hour period.

Other:

A serious event not otherwise defined in the above definitions which is fatal, life-threatening, resulted in permanent disability, required hospitalization or prolongation of hospital stay. Also, a patient related low flow condition causing a red heart alarm (e.g. dehydration).

Suspected Device Malfunction/Failure:

An instance when any component of the system fails to perform its intended function. Losses of the display, inability to operate on batteries, or pump stoppage are examples. Event consequences will be captured on the case report form and will include: hemodynamic compromise, re-operation, death, urgent transplant or initiation of inotropes.