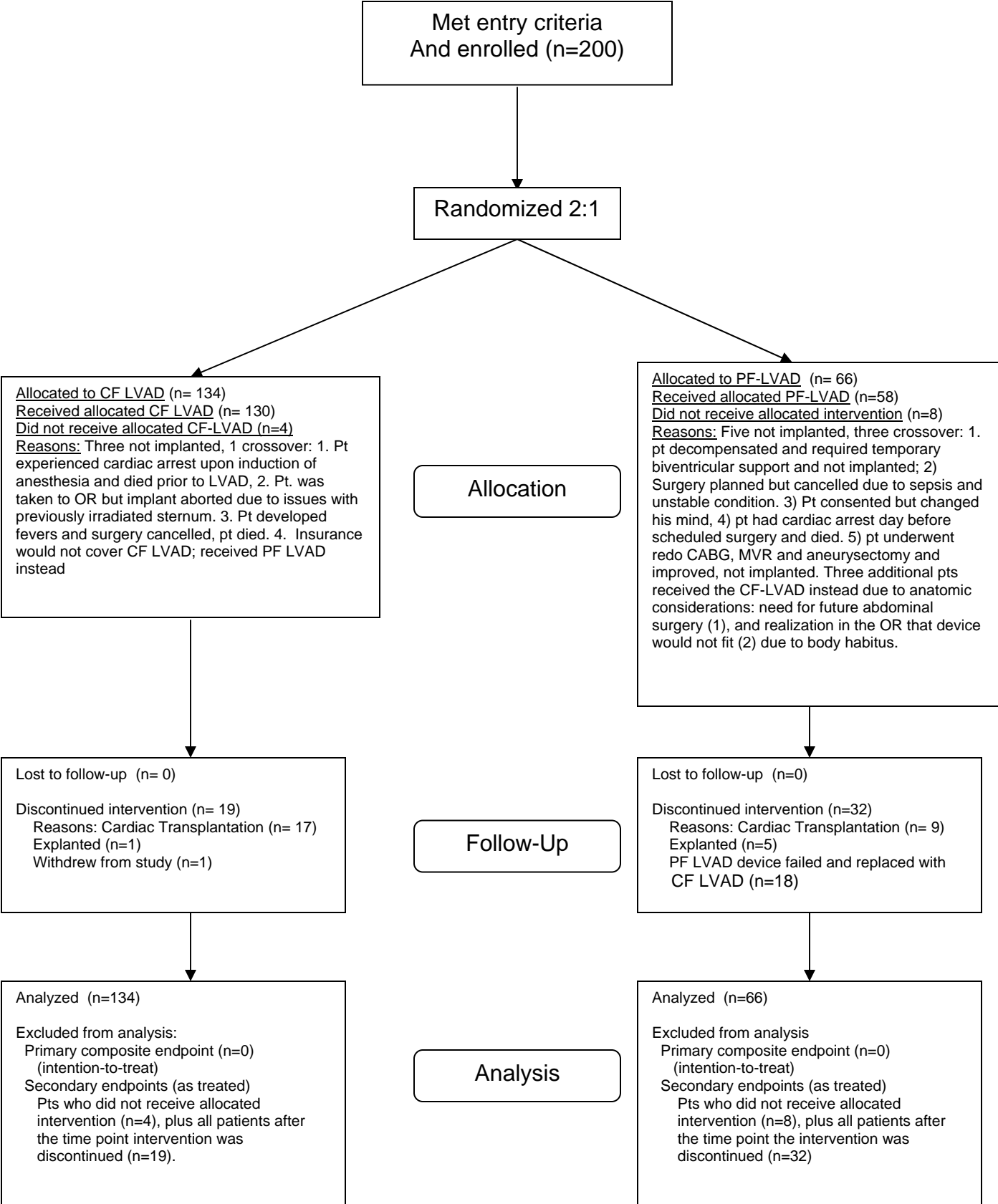


Supplementary Appendix

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

Supplement to: Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;361:2241-51. DOI: 10.1056/NEJMoa0909938.

Consort Flowchart



Study Enrollment Criteria

Study inclusion criteria included:

1. Patient or their legal representative has signed an informed consent.
2. ≥ 18 years of age.
3. $BSA \geq 1.5m^2$ for a patient to be randomized between HM XVE and HM II. If $BSA < 1.5 m^2$ and $\geq 1.2 m^2$, the patient must meet the remaining criteria and can be enrolled in the Small Size Cohort.
4. Patients with advanced heart failure symptoms (Class IIIB or IV) who are: (patient must meet one of the following)
 - i. On OMM, including dietary salt restriction, diuretics, digitalis, beta-blockers, spironolactone and ACE inhibitors, for at least 45 out of the last 60 days and are failing to respond; or
 - ii. In Class III or Class IV heart failure for at least 14 days, and dependent on intra aortic balloon pump (IABP) for 7 days and/or inotropes for at least 14 days; or
 - iii. Treated with ACE inhibitors or beta-blockers for at least 30 days and found to be intolerant.
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. Ineligible for cardiac transplant.
7. $VO_{2max} \leq 14$ ml/kg/min or $<50\%$ of predicted VO_{2max} with attainment of anaerobic threshold (AT), if not contra-indicated due to IV inotropes, angina or physical disability.
8. LVEF is $\leq 25\%$.

Study Exclusion Criteria Included

1. Etiology of heart failure is due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, active myocarditis 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 kg/m².
5. Positive pregnancy test if female of childbearing age.

6. Presence of mechanical aortic valve that will not be converted to a bioprosthesis at time of LVAD implant.
7. History of cardiac transplant or cardiomyoplasty.
8. Platelet count $\leq 50,000$.
9. Evidence of an untreated aortic aneurysm ≥ 5 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 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. INR ≥ 2.5 , which is not due to anti-coagulant therapy, or Plavix administration within 5 days.
14. Evidence of intrinsic hepatic disease as defined by liver enzyme values (AST or ALT or total bilirubin) that are > 5 times the upper limit of normal, or biopsy proven liver cirrhosis.
15. History of severe COPD or severe restrictive lung disease.
16. Fixed pulmonary hypertension with a PVR ≥ 8 Wood units that is unresponsive to pharmacological intervention.
17. History of a stroke within 90 days prior to enrollment, or a history of cerebral vascular disease with significant ($> 80\%$) extra cranial stenosis.
18. Serum creatinine ≥ 3.5 mg/dl or the need for chronic renal replacement therapy (e.g. chronic dialysis).
19. Significant peripheral vascular disease accompanied by rest pain or extremity ulceration.
20. The patient has moderate to severe aortic insufficiency without plans for correction during pump implantation surgery.
21. Participation in any other clinical investigation that is likely to confound study results or affect study outcome.
22. Patient is receiving a calcium channel blocker (except amlodipine), or a Type I or Type III antiarrhythmic (except amiodarone) within 28 days prior to enrollment.
23. Any condition, other than heart failure, that could limit survival to less than 3 years.

Reasons Not Transplant candidate at enrollment

	CF LVAD (n=134)	PF LVAD (n=66)	Total (n=200)
Age	37 (28%)	18 (27%)	55 (28%)
Age and Cancer	5 (4%)	2 (3%)	7 (4%)
Age and IDDM	1 (1%)	2 (3%)	3 (2%)
Age and COPD	1 (1%)	0 (0%)	1 (1%)
Age and Patient refuses transplant	1 (1%)	0 (0%)	1 (1%)
Age and Pulmonary hypertension	1 (1%)	0 (0%)	1 (1%)
Age and Renal Failure	2 (1%)	1 (2%)	3 (2%)
Age and Renal Insufficiency	1 (1%)	0 (0%)	1 (1%)
Age and Multiple Co-morbidities	1 (1%)	2 (3%)	3 (2%)
IDDM (insulin dependent diabetes mellitus)	8 (6%)	1 (2%)	9 (5%)
IDDM and Obese	1 (1%)	1 (2%)	2 (1%)
IDDM and PVD	0 (0%)	1 (2%)	1 (1%)
IDDM and Patient refuses transplant	0 (0%)	1 (2%)	1 (1%)
IDDM and Multiple Co-morbidities	1 (1%)	3 (5%)	4 (2%)
Renal Failure	5 (4%)	2 (3%)	7 (4%)
Renal Failure and Compliance Issues	1 (1%)	0 (0%)	1 (1%)
Renal Failure and Obese	2 (1%)	0 (0%)	2 (1%)
Renal failure and Patient refuses transplant	1 (1%)	0 (0%)	1 (1%)
Renal Insufficiency	1 (1%)	1 (2%)	2 (1%)
Obesity	12 (9%)	2 (3%)	14 (7%)
Obesity and COPD	1 (1%)	0 (0%)	1 (1%)
Obesity and CRI	1 (1%)	0 (0%)	1 (1%)
Obesity and Multiple other Co-morbidities	1 (1%)	0 (0%)	1 (1%)
Recent history of Cancer	9 (7%)	8 (12%)	17 (9%)
Social Issue / Compliance	7 (5%)	6 (9%)	13 (7%)
Pulmonary Hypertension	5 (4%)	1 (2%)	6 (3%)
Pulmonary HTN and Obese	1 (1%)	1 (2%)	2 (1%)
Pulmonary HTN and Compliance Issue	1 (1%)	0 (0%)	1 (1%)
Pulmonary HTN and PRA	2 (1%)	0 (0%)	2 (1%)
Pt Refuses Transplant	8 (6%)	2 (3%)	10 (5%)
PVD	3 (2%)	2 (3%)	5 (3%)
PVD and Obese	0 (0%)	1 (2%)	1 (1%)
PVD and Pulmonary function	1 (1%)	0 (0%)	1 (1%)
PVD and Diabetic	1 (1%)	0 (0%)	1 (1%)
PVR	3 (2%)	0 (0%)	3 (2%)
Hepatitis C	2 (1%)	1 (2%)	3 (2%)
PRA 100%	1 (1%)	0 (0%)	1 (1%)
PRA and CRI	1 (1%)	0 (0%)	1 (1%)
PRA and Compliance issues	1 (1%)	0 (0%)	1 (1%)
Insufficient insurance coverage	0 (0%)	2 (3%)	2 (1%)
Other*	1 (1%)	5 (8%)	6 (3%)
Other Multiple Co-morbidities	2 (1%)	0 (0%)	2 (1%)

*Other reasons include retinopathy, cachexia, debilitated

Detailed Baseline characteristics (Mean \pm SD or N (percent))

Characteristic	HeartMate II (n=134)	HeartMate XVE (n=66)	p- value
Age (yr)	62 \pm 12	63 \pm 12	0.81
Male (%)	108 (81%)	61 (92%)	0.037
Caucasian/African American (%)	101 (75%)/ 24 (18%)	48 (73%)/ 16 (24%)	0.39
Body mass index (kg/m ²)	28.2 \pm 5.5	28.2 \pm 5.6	0.99
Body surface area (m ²)	2.0 \pm 0.3	2.0 \pm 0.3	0.54
Ischemic etiology of heart failure (%)	88 (66%)	45 (68%)	0.75
Left-ventricular ejection fraction (%)	17 \pm 5.5	16.8 \pm 5.4	0.81
Arterial blood pressure (mm Hg)			
Systolic	103.6 \pm 14.4	103.8 \pm 17.5	0.93
Diastolic	60.8 \pm 13.2	60.6 \pm 12.1	0.94
Pulmonary-capillary wedge pressure (mmHg)	24 \pm 8.4	23.7 \pm 8.8	0.82
Cardiac index (liters/min/m ²)	2 \pm 0.6	2.1 \pm 0.6	0.36
Heart rate (beats per minute)	84 \pm 15	83 \pm 12	0.64
Pulmonary artery pressure (mm Hg)			
Systolic	54.3 \pm 13.8	52.7 \pm 12.8	0.43
Diastolic	25.6 \pm 8.2	25.7 \pm 8.4	0.94
Mean	36.2 \pm 9.5	35.8 \pm 9.5	0.78
Pulmonary vascular resistance (Wood Units)	3.3 \pm 1.6	3.3 \pm 1.9	0.98

Central venous pressure (mmHg)	12.7 ± 6	13.2 ± 8	0.67
NYHA class IV	95 (75%)	43 (78%)	0.94
Class IIIA	27 (21%)	11 (20%)	
Class IIIB	4 (3%)	1 (2%)	
Serum sodium (mmol/liter)	134.7 ± 4.3	133.9 ± 6	0.31
Serum albumin (g/dL)	3.3 ± 0.6	3.3 ± 0.6	0.64
Pre-albumin (mg/dL)	18.2 ± 7.4	20.2 ± 13.4	0.29
Cholesterol (mg/dL)	121.5 ± 35.6	114.5 ± 29.5	0.21
Serum creatinine (mg/dL)	1.6 ± 0.6	1.8 ± 0.7	0.08
Blood Urea Nitrogen (mg/dL)	37.7 ± 25.3	37.3 ± 20.6	0.93
ALT (IU/L)	38.6 ± 37.1	53 ± 69.1	0.12
AST (IU/L)	36.3 ± 46.7	39.2 ± 34.4	0.66
Total Bilirubin (mg/dL)	1.2 ± 0.7	1.3 ± 0.8	0.70
LDH (mg/dL)	336 ± 246	317 ± 223	0.61
Hematocrit (%)	34.7 ± 5	34.4 ± 4.9	0.68
White blood count (x 1000)/ml	7.9 ± 3.1	8.1 ± 2.7	0.69
Platelets (1000/ml)	207 ± 79.6	225 ± 90	0.15
International Normalized Ratio	1.3 ± 0.3	1.3 ± 0.3	0.53
Concomitant Medications			
Intravenous inotrope agents	103 (77%)	55 (83%)	0.36
Diuretics	123 (92%)	57 (86%)	0.32

ACE inhibitors	43 (32%)	22 (33%)	0.87
Antiotension II receptor antagonists	12 (9%)	3 (5%)	0.39
Beta-blockers	71 (53%)	38 (58%)	0.55
Digoxin	67 (50%)	29 (44%)	0.45
Hydrazaline	19 (14%)	9 (14%)	1.00
Amiodarone	51 (38%)	38 (58%)	0.01
Heparin	54 (40%)	29 (44%)	0.65
Warfarin	7 (5%)	5 (8%)	0.54
Aspirin	55 (41%)	29 (44%)	0.65
Biventricular pacemaker	85 (63%)	39 (59%)	0.64
ICD	111 (83%)	52 (79%)	0.56
IABP	30 (22%)	15 (23%)	1.00
Mechanical ventilation	9 (7%)	6 (9%)	0.57
Destination Therapy Risk Score ¹⁶			
Mean ± SD	10.4 ± 5.4	9.9 ± 4.7	0.78
% pts high/very high risk	24 (18%)	5 (8%)	0.056

SD – standard deviation, RVSWI - right ventricular stroke work index, NYHA – New York Heart Association, AST - serum aspartate aminotransaminase, ALT - serum alanine aminotransaminase, LDH – lactate dehydrogenase, ACE - angiotensin converting enzyme, ICD - implantable cardioverter defibrillator, IABP - intra-aortic balloon pump.

Anticoagulation Guidelines

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.

Definition of Adverse Events

Bleeding:

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

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

Localized Non-device 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.

Device-related Infections (Percutaneous Site, Pump Pocket, Pump Housing, Inflow or Outflow Tract Infection)

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.

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.

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.

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.

All Adverse Events (As Treated Analysis) for patients receiving continuous-flow (DF) or pulsatile-flow (PF) left ventricular assist devices (LVAD).

	CF LVAD (n=133) [211 pt-years]			PF LVAD (n=59) [41 pt-years]			Risk Ratio [95% CI]
	# Pts (%)	# Events	Events/ pt yr	Pts (%)	# Events	Events/ pt yr	
Pump Replacements	12 (9%)	13	0.06	20 (34%)	21	0.51	0.12 [0.06-0.26]***
Bleeding	118 (89%)	398	1.89	51 (86%)	113	2.76	0.69 [0.47-1.03]
Bleeding requiring PRBC ¹	108 (81 %)	349	1.66	45 (76 %)	101	2.45	0.68 [0.46-1.02]
Bleeding requiring surgery	40 (30%)	49	0.23	9 (15%)	12	0.29	0.80 [0.39-1.64]
Stroke	24 (18%)	27	0.13	8 (14%)	9	0.22	0.59 [0.26-1.35]
Ischemic	11 (8%)	12	0.06	4 (7%)	4	0.10	0.59 [0.18-1.92]
Hemorrhagic	15 (11%)	15	0.07	5 (8%)	5	0.12	0.59 [0.20-1.71]
Other Neurological ²	29 (22%)	35	0.17	10 (17%)	12	0.29	0.57 [0.28-1.20]
Local Infection	65 (49%)	160	0.76	27 (46%)	55	1.33	0.57 [0.36-0.90]**
Percutaneous Lead Infection	42 (32%)	80	0.38	16 (27%)	25	0.61	0.63 [0.36-1.10]
Pump Pocket Infection	12 (9%)	19	0.09	8 (14%)	10	0.24	0.37 [0.16-0.86]*
Pump Housing Infection	1 (1%)	1	0.00	2 (3%)	2	0.05	0.10 [0.01-1.11]*
Any device infection	47 (35 %)	100	0.48	21 (36%)	37	0.90	0.53 [0.32-0.88] *
Sepsis	48 (36%)	81	0.39	26 (44%)	46	1.11	0.35 [0.21-0.57]***
Right Heart Failure	31 (23%)	34	0.16	19 (32%)	22	0.53	0.30 [0.16-0.57]***
Inotropes Only	27 (20%)	29	0.14	16 (27%)	19	0.46	0.30 [0.15-0.59]***
RVAD ³	5 (4%)	5	0.02	3 (5%)	3	0.07	0.33 [0.08-1.43]
Peripheral TE	14 (11%)	21	0.10	8 (14%)	8	0.19	0.52 [0.21-1.25]
Respiratory Failure	50 (38%)	65	0.31	24 (41%)	33	0.80	0.39 [0.23-0.66]***
Cardiac Arrhythmias	75 (56%)	145	0.69	35 (59%)	54	1.31	0.53 [0.33-0.83]**
Renal Failure	21 (16%)	21	0.10	14 (24%)	14	0.34	0.30 [0.14-0.63]***
Hepatic Dysfunction	3 (2%)	3	0.01	0 (0%)	0	0.00	-
Device Thrombosis	5 (4%)	5	0.02	0 (0%)	0	0.00	-
Hemolysis	5 (4%)	5	0.02	0 (0%)	0	0.00	-
Psychological	8 (6%)	11	0.05	4 (7%)	4	0.10	0.54 [0.16-1.78]
Myocardial Infarction	0 (0%)	0	0.00	1 (1%)	1	0.02	-
Rehospitalizations ⁴	107 (94%)	524	2.64	42 (96%)	148	4.65	0.62 [0.41- 0.93]*

¹Packed red blood cells, ²Includes transient ischemic attacks (TIA) and non-stroke neurological events. ³Right ventricular assist device;

⁴Calculated on patient-years after hospital discharge