

**21 CFR §814.20(b)(3)**  
**SUMMARY OF SAFETY AND EFFECTIVENESS**

**SynCardia Systems, Inc. CardioWest Total Artificial Heart**  
**Premarket Approval (PMA) Application P030011**

**SynCardia Systems, Inc.**  
**1992 E. Silverlake Road**  
**Tucson, Arizona 85713**

**I. GENERAL INFORMATION**

Device Generic Name:	Total Artificial Heart
Device Trade Name:	CardioWest Total Artificial Heart
Applicant's Name and Address:	SynCardia Systems, Inc. 1992 East Silverlake Road Tucson, Arizona 85713
PMA Application Number:	P030011
Date of Panel Recommendation:	TBD
Date of Notice of Approval to the Applicant:	TBD

**II. INDICATIONS FOR USE**

The SynCardia Systems, Inc., CardioWest Total Artificial Heart (hereinafter called the TAH) is indicated for use as a bridge to transplantation in cardiac transplant-eligible candidates at risk of imminent death from non-reversible biventricular failure. The TAH is intended for use inside the hospital.

**III. CONTRAINDICATIONS**

Patients who are not cardiac transplant candidates.

Patients who have body surface areas <1.7m<sup>2</sup>.

**IV. WARNINGS AND PRECAUTIONS**

All Warnings and Precautions can be found in the attached labeling.

**V. DEVICE DESCRIPTION**

The SynCardia CardioWest TAH system is a pulsatile biventricular device that is placed after the native ventricles are excised. The implantable device consists of two artificial ventricles, each made of a semi-rigid polyurethane housing with four flexible polyurethane diaphragms separating the blood chamber from the air chamber. These diaphragms allow the ventricles to fill and then eject blood when compressed by air from the external drive console. Mechanical valves mounted in the inflow (27 mm) and outflow (25 mm) ports of each artificial ventricle control the direction of blood flow. The maximum dynamic stroke volume of each artificial ventricle is 70 ml, which allows for generating a flow rate up to 9.5 l/min. The right artificial ventricle is connected via the right atrial inflow connector to the right atrium and via the pulmonary artery outflow cannulae to the pulmonary artery. The left artificial ventricle is connected via the left atrial inflow connector to the left atrium, and via the aortic outflow cannulae to the aorta. Each artificial ventricle's driveline

conduit is tunneled through the chest. The driveline conduit is covered with velour fabric on its external surface to promote tissue growth. The right and left driveline conduits are attached to seven-foot drivelines that connect to the back of the external drive console.

The console includes a monitoring computer that provides noninvasive diagnostic and monitoring information to the user. Device pumping rate, noninvasive dynamic stroke volumes, and calculated cardiac outputs are displayed on a beat-to-beat basis. Drive pressure and flow waveforms, along with cardiac output trends are provided. Patient related alarms (e.g., low cardiac output) are also displayed on the computer screen. A separate alarm panel on the console provides information on critical drive pressure and backup systems. All alarms generate audio and visual feedback to the user.

A backup air supply (two air tanks) and electrical power (backup power supply and console battery) are automatically activated if the external compressed air and /or AC power are interrupted. This can occur during patient transport or in the event of a failure in the hospital's air or electrical supply.

The controller is the major component of the external console, and supplies pulses of pneumatic pressure to the right and left drivelines, which connect into the air chambers of the respective implanted artificial ventricles. These pulses cause the diaphragms to distend and thereby eject blood from the right artificial ventricle into the pulmonary circulation and from the left artificial ventricle into the systemic circulation.

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

There are no alternate medical or surgical therapies available for patients in end stage biventricular heart failure, other than a heart transplant. These patients have received maximum medical and/or surgical therapy and require intensive monitoring because they are dependent on inotropic support, are hemodynamically unstable, and are within hours or days of dying. These patients have failed medical therapy and require intensive care monitoring because they are dependent on inotropic support and are unstable. Combinations of ventricular assist devices (VADs) have been used to support both the right and left sides of the heart to bridge the patients to transplant; however there are no conclusive data demonstrating the safety and efficacy of specific combinations. One device, the Thoratec Ventricular Assist Device System, is approved for use as a bi-VAD device, but is only designed to assist the ventricles. The TAH is the only device tested that replaces a patient's native ventricles and valves so as to completely take over pumping of blood to both the pulmonary and systemic circulation, and bridge the patient to transplant.

## **VII. MARKETING HISTORY**

Under the authority of 21 CFR §801(e), SynCardia has permission to export, and has distributed the CardioWest Total Artificial Heart to Canada, France, and Germany. The CardioWest TAH has a CE mark from NEMKO, issued October 2001, CE Mark 0470. The SynCardia CardioWest TAH has not been withdrawn from marketing for any reason related to safety and effectiveness of the device.

## VIII. ADVERSE EFFECTS

Adverse events collected for all 81 core patients while on the TAH device are presented in descending order below. The adverse events represent 17.6 device years of experience for an overall event rate of 1.9 events per month while on the device awaiting transplant. By comparison, 89 events occurred in 31 of the control patients (88.9%) during a total of 299 days awaiting transplant, for an overall event rate of 8.9 events per month while waiting for transplant.

**Table 1**  
**Incidence of Adverse Events in Core Patients During Device Implantation,**  
**in Decreasing Order of Frequency**  
**(Represents 17.6 years or 6411 days on the device)**

Adverse Event	Number of Events	Number (%) of Patients n=81
Any Adverse Event	400	76 (93.8%)
Infection	125	58 (71.6%)
Bleeding	55	34 (42.0%)
Respiratory Dysfunction	44	24 (29.6%)
Hepatic Dysfunction	30	29 (35.8%)
Neurological Event	26	20 (24.7%)
Renal Dysfunction	23	21 (25.9%)
Operation	18	17 (21.0%)
Device Malfunction	18	15 (18.5%)
Peripheral Thromboembolism	14	9 (11.1%)
Reduced Blood Pressure	13	12 (14.8%)
Cardiac Index	11	7 (8.6%)
Technical/Procedural	11	3 (3.7%)
Fit Complication	5	5 (6.2%)
Hemolysis	3	3 (3.7%)
Miscellaneous	3	3 (3.7%)

Infections were the largest contributing category to overall adverse events. The majority of infections (114/125 [91.2%]) did not affect patient outcome. Most were genitourinary (33/125 [26.4%]), followed by respiratory infections which occurred the first few weeks

following implant (30/125 [24.0%]). Driveline infections (17/125 [13.6%]) were predominantly superficial skin infections treated with routine dressing changes.

Bleeding was reported only for the core patients, and was related to the surgical procedure. In some cases, reoperations (18) were also required for excessive bleeding around the heart or lungs. Patients were fully anticoagulated at the time of TAH implantation and were maintained on an anticoagulation regimen throughout the implantation period. Forty four [80.0%] of the 55 bleeding events occurred during the first 3 weeks after implant.

Respiration dysfunction was also surgically related with most events (31/44 [70.5%]) occurring during the first 3 weeks following the implant surgery. Hepatic and renal dysfunction occurred in the first 3 weeks following the implant. By 4 weeks, hepatic and renal markers were at normal levels.

Twenty six neurologic events occurred in 20 core patients. Eleven strokes occurred in ten core patients during the implant period. One stroke temporarily affected patient outcome, and that patient was successfully transplanted after 332 days on the device. Other neurologic events were encephalopathy (5/26 [19.2%]), seizures (4/26 [15.4%]), transient ischemic attacks (4/26 [15.4%]), loss of consciousness (1/26 [3.8%]) and related to metabolic imbalances (1/26 [3.8%]).

Fifteen patients (18.5%) had 18 device malfunctions; most were kinks from patients rolling over or sitting on their drivelines (11/18 [61.1 %]), or driveline leaks (5/18 [27.7%]). A change in manufacturing eliminated the cause of driveline leaks. One malfunction, a diaphragm tear, was a primary cause of death. The patient had hemodynamic insufficiency, was carefully monitored, and on post-operative day 115, a clot caused cardiac output to decrease, requiring removal of a large hemo-pneumothorax. The family refused another implant and the patient developed multi-organ failure and died on day 124. Although extensively investigated, the cause of the failure was never determined and could never be duplicated. There have been no additional instances of diaphragm tears found during production or experienced clinically, since the incident.

Reduced blood pressure was secondary to sepsis (7/14 [50.5%]), volume depletion 5/14 [35.7%]), medication (1/14 [7.1%]) and hematuria (1/14 [7.1%]).

All technical/procedural events (11/11 [100%]) were related to a central catheter obstruction of the artificial valve within the TAH. Labeling has been modified to include a warning based on these clinical events. The warning advises physicians to not allow any catheter to get near the left or right inflow valves.

## IX. SUMMARY OF NON-CLINICAL LABORATORY TESTS

### A. Biocompatibility/Sterilization

The implantable hearts were sterilized by the validated EtO sterilization cycle, extracted and tested in accordance with ISO 10993, *Biological Evaluation of Medical Devices*, test methods, and in accordance with Good Laboratory Practices. Results of the testing are summarized below.

**Table 2**  
**Biocompatibility Testing**

Test Performed	Result
Cytotoxicity	Non-cytotoxic
Acute Systemic Toxicity	No systemic toxicity
Subchronic Toxicity	No histological evidence of subchronic toxicity
Ames Mutagenicity	Non-mutagenic
Chromosomal Aberration Assay	No induced chromosomal aberrations
Mouse micronucleus Mutagenicity	Non-mutagenic
Pyrogen	Nonpyrogenic
Sensitization	Non-sensitizing
Hemocompatibility	Hemocompatible

### B. In-vitro Studies

#### 1. *In-vitro* Characterization

*In-vitro* characterization of the TAH on a mock circulatory loop demonstrated the performance of TAH under normal, hypotensive and hypertensive simulated operating conditions as indicated below.

**Table 3**  
**Conditions for Mock Circulation Testing**

Setting/Parameter	Hypotensive	Normal	Hypertensive
BPM $\pm$ 5	80	120	140
% systole $\pm$ 5	55	50	60
LDP $\pm$ 15 mmHg	150	200	280
RDP $\pm$ 15 mmHg	40	75	135
Vacuum $\pm$ 5 mm Hg	none	10	15

The TAH provided a range from 2.6-9.5 l/min flow, which is sufficient to support total circulation under the expected clinical conditions.

## 2. *In-vitro* System Testing

Laboratory testing was performed to demonstrate that the TAH system met its intended functional specifications. Testing included pull tests and torque tests on the ventricle-to-connector joints and drivelines, and sterility and packaging testing on the implantable components of the system. Console testing included controller performance of alarms, system connections, battery longevity, electrical safety and electro-magnetic compatibility. Software verification and validation was performed and back-up air and power performance were verified under simulated use conditions.

### C. Reliability

The purpose of reliability testing is to determine with reasonable assurance, how long a given device will perform as intended, without failure.

Three separate sets of *in vitro* reliability testing were conducted. In one test, four TAH units were run for a period of 180 days. During this time there were no failures or abnormalities observed.

In a second *in vitro* reliability trial initiated in December 1998, four TAH units were tested in a “run to failure” study design and are ongoing. To date, there have been no failures or abnormalities observed.

A third test was initiated using three TAH units which had expired their 3 year sterilization expiration date. This provided information about the effects of long-term storage on the fatigue resistance properties of the TAH. To date, there have been no failures or abnormalities observed.

In conclusion, a total of eleven units have been run for various lengths of time over the last six years with no device-related failures. The cumulative number of days used for calculation was 6715 and there have been no failures or signs of appreciable wear observed. When the 11 units are used to calculate reliability with a 90% confidence, the reliability at 30, 60 and 365 days is as reported in the table below.

**Table 4**  
**Reliability Test Results with 90% Confidence**

# days run	MTBF*	Reliability in number of days run		
		30	60	365
6715	2916	0.99	0.98	0.88

## **X. SUMMARY OF CLINICAL STUDIES**

### **A. Study Objective**

The purpose of this study was to demonstrate that the CardioWest Total Artificial Heart is safe and effective in providing circulatory support as a bridge to cardiac transplantation in patients with non-reversible bi-ventricular failure. Bridge to transplant is defined as the use of a circulatory support device to maintain viability for transplantation until a donor organ is procured.

### **B. Study Design**

The study was approved under IDE G920101 as a non-randomized, multi-centered trial with both historical and concurrent controls. Patients were transplant candidates who were at risk of imminent death from non-reversible biventricular heart failure. The overall objective of this study was to determine if the TAH was safe and effective for bridging to cardiac transplantation. A total of 130 patients were enrolled. Of these, 81 formed the core implant group and 35 patients who met the inclusion/exclusion criteria but for whom the device was not available (32 historically and 3 prospectively), were enrolled as controls. An additional 14 patients did not meet study entrance criteria and were considered an out-of-protocol cohort, treated under compassionate use. IRB acknowledgments were obtained for each patient. The data used to demonstrate safety and effectiveness were collected from patients enrolled at five U.S. investigational sites.

#### *1. Effectiveness Parameters*

Treatment success was defined as patients who, at 30 days post transplant, were 1) alive; 2) New York Heart Association Class I or II; 3) not bedridden; 4) not ventilator dependent; and 5) not requiring dialysis. Overall survival, hemodynamics and kidney and liver end organ function were secondary effectiveness endpoints.

#### *2. Safety Parameters*

Patients were clinically assessed and adverse events were evaluated for safety.

### **C. Study Protocol**

#### *1. Inclusion Criteria*

Patients who met all of the following inclusion criteria were eligible for the study:

- ?? Signed informed consent
- ?? Eligible for Transplant
- ?? New York Heart Association Functional IV

?? Body surface area 1.7-2.5 m<sup>2</sup>, or have a distance between the sternum and the 10<sup>th</sup> anterior vertebral body measured by computed tomography imaging (CT scan) = 10 cm.

?? Hemodynamic insufficiency demonstrated by A or B below:

A: Cardiac index =2.0 l/min/M<sup>2</sup> and one of the following:  
Systolic arterial pressure =90 mm Hg  
Central venous pressure =18 mm Hg

B: Two of the following:  
Dopamine = 10 µg/kg/min  
Dobutamine = 10 µg /kg/min  
Epinephrine = 2 µg /kg/min  
Isoproterenol =2 µg /kg/min  
Amrinone = 10 µg /kg/min  
Other drugs at maximum levels  
Intra-aortic balloon pump (IAPB)  
Cardiopulmonary bypass (CPB)

## 2. Exclusion Criteria

Patients with any of the following conditions were excluded from the study:

- ?? Use of any ventricular assist device
- ?? Pulmonary Vascular Resistance = 8 Wood (640 Dynes-sec/cm<sup>5</sup>).
- ?? Dialysis in previous 7 days
- ?? Serum Creatinine = 5 mg/dl
- ?? Cirrhosis with Bilirubin = 5 mg/dl
- ?? Cytotoxic antibody = 10%

## 3. Treatment Procedures

All patients were screened for study eligibility. The treatment group met eligibility criteria within 48 hours of the implant procedure, signed an informed consent and received a TAH implant. Control patients were considered eligible when they met the eligibility criteria and were considered at risk of imminent death.

## 4. Term of Study

Patients were followed through the primary endpoint of 30 days post transplant, and then monitored for survival annually.

**D. Description of Control Population**

The control group was initially identified by retrospective review during a time period when the TAH was not available to the participating centers. Prospective study participants were included if subjects who qualified for TAH implantation refused the option. There were 22 control patients collected retrospectively and an additional 3 patients were found prospectively during the clinical trial. Finally, the UNOS lists from the three primary implanting centers were 100% reviewed at the conclusion of the trial to capture any patients who were not prospectively identified over the nine-year study period. This yielded an additional 10 retrospective patients, providing the total of 35 control patients (32 retrospective and 3 prospective). The control patients met the identical entrance criteria as the implant group.

**E. Description of Study Population**

There were 81 patients entered into the core treatment group. The patients were predominantly male (86%) with average age of 51 (range 16-67), and average body weights and surface areas of 85.3 kg and 2.0 m<sup>2</sup>. All patients were NYHA functional Class IV at the time of enrollment. The etiology of the heart disease was ischemic (53%) or idiopathic (47%).

No gender requirements were identified for inclusion into the trial. The United Network for Organ Sharing (UNOS) August 1, 2001 database of all patients receiving heart transplants, heart-lung transplants or multiple organ transplants, divides gender into 73.3% males and 26.7% females for cardiac transplants.. For the 64 patients who received a heart transplant in this trial, 86.4% were males vs. 13.6% females, indicating similar characteristics as the UNOS data.

Baseline characteristics for the core patients are provided in the table below.

**Table 5**  
**Baseline Demographics, Risk Factors and Clinical Characteristics**  
**for Core Implant Patients**

Characteristic	n=81
Age (years) Mean $\pm$ SD	51.1 (10.3)
Male	70 (86.4%)
Height (mean in cm) $\pm$ SD	176.2 (11.1)
Weight (mean in kg) $\pm$ SD	85.3 (13.2)
BSA (mean as m <sup>2</sup> )	2.0 (0.18)
NYHA Class IV	81 (100.0%)
Cardiac index L/min/m <sup>2</sup> $\pm$ SD	1.9 (0.5)
Etiology – Ischemic	43 (53.1%)
Etiology -Non-ischemic (idiopathic)	38 (46.9%)
History of smoking	44 (54.3%)
History of excessive alcohol use	37 (45.7%)
Hypertensive	26 (32.1%)
Prior cardiac arrest	30 (37.0%)
Anticoagulated on entry	38 (46.9%)
Insulin-dependent Diabetes Mellitus	5 (6.2%)
Non- insulin-dependent Diabetes Mellitus	15 (18.5%)
Entry on Cardiopulmonary bypass	15 (18.5%)
Entry on intra-aortic balloon pump	29 (35.8%)
Entry with ventilator	34 (42.0%)
Entry obtunded/drowsy	28 (34.6%)
Prior mediastinal surgery	31 (38.3%)
Prior percutaneous angioplasty	12 (14.8%)
Pacemaker	10 (12.3%)
Automatic implantable cardioverter defibrillator	24 (29.6%)

Baseline hemodynamics, hematology and blood chemistry for the core implant group is presented below. At entry, 15 patients were supported by cardiopulmonary bypass and 29 patients were supported on intra-aortic balloon pumps to maintain hemodynamics.

**Table 6**  
**Baseline Hemodynamics – Core Implant Patients**

<b>Hemodynamic Measurement</b>	<b>Mean Value (SD) n = 81</b>
Cardiac Index (L/min/M <sup>2</sup> )	1.9 (0.5) n = 65
Cardiac Output (L/min)	3.9 (1.1) n = 65
Systemic Vascular Resistance (dyne-sec/cm <sup>5</sup> )	1108.9 (393.7) n = 68
Pulmonary Vascular Resistance (dyne-sec/cm <sup>5</sup> )	221.7 (116.8) n = 78
Heart Rate (bpm)	101.3 (20.7) n = 81
Systolic Arterial Pressure (mm Hg)	92.8 (15.2) n = 79
Mean Arterial Pressure (mm Hg)	68.1 (9.1) n = 79
Pulmonary Artery Systolic Pressure (mm Hg)	55.2 (13.5) n = 72
Pulmonary Artery Mean Pressure (mm Hg)	41.1 (10.8) n = 72
Pulmonary Capillary Wedge Pressure (mm Hg)	29.6 (10.6) n = 68
Central Venous Pressure (mm Hg)	19.7 (6.9) n = 77
Organ Perfusion Pressure (mm Hg)	48.6 (10.9) n = 75

**Table 7**  
**Baseline Blood Chemistry and Hematology**  
**Core Implant Patients**

<b>Chemistry/Hematology Measurement</b>	<b>Mean Value (SD) n = 81</b>
<b>Chemistry</b>	
Sodium (mEq/L)	132.0 (6.7) n = 79
Potassium (mEq/L)	4.4 (0.9) n = 80
Chloride (mEq/L)	96.1 (6.7) n = 79
Blood Urea Nitrogen (mg/dL)	36.2 (18.7) n = 79
Creatinine (mg/dL)	1.7 (0.6) n = 81
Total Bilirubin (mg/dL)	2.0 (1.3) n = 79
SGOT (IU/L)	189.9 (773.1) n = 77
<b>Hematology</b>	
White Blood Cell Count ( $10^3/\mu\text{L}$ )	11.4 (4.1) n = 80
Red Blood Cell Count ( $10^6/\mu\text{L}$ )	3.8 (0.7) n = 80
Hematocrit (%)	33.7 (6.1) n = 80
Platelet Count ( $10^3/\mu\text{L}$ )	213.0 (93.6) n = 77
Plasma Free Hemoglobin (mg/dL)	11.5 (16.0) n = 64
<b>Coagulation Panel/Cytotoxicity</b>	
Prothrombin Time (sec)	16.4 (4.4) n = 79
International Normalization Ratio (INR)	2.0 (1.5) n = 79
Partial Thromboplastin Time (sec)	37.3 (12.7) n = 75
Fibrinogen (mg/dL)	467.4 (198.6) n = 62
Cytotoxic Antibody (%)	0.0 (0.3) n = 76

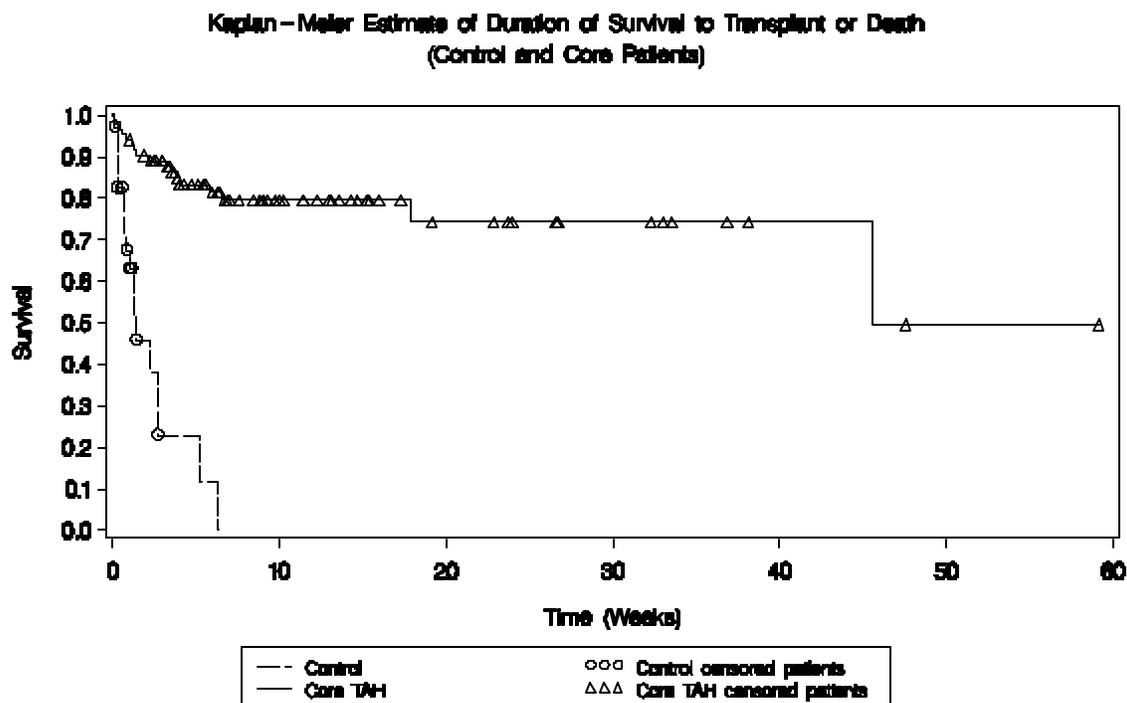
Core patients had significantly longer times to transplant or death compared to those who did not receive a total artificial heart (controls). The mean core patient wait was 79 days, over 9 times longer than the mean control time, providing significantly more time for implant patients to obtain a donor heart.

**Table 8**  
**Time to Transplant or Death**

Time	Statistic	Control n = 35	Core n = 81
Duration (days)	Mean (SD)	8.5 (9.5)	79.1 (83.9)
	Median	6.0	47.0
	Min-Max	1.0 - 44.0	1.0 - 414.0
Total Duration (days)		299	6411

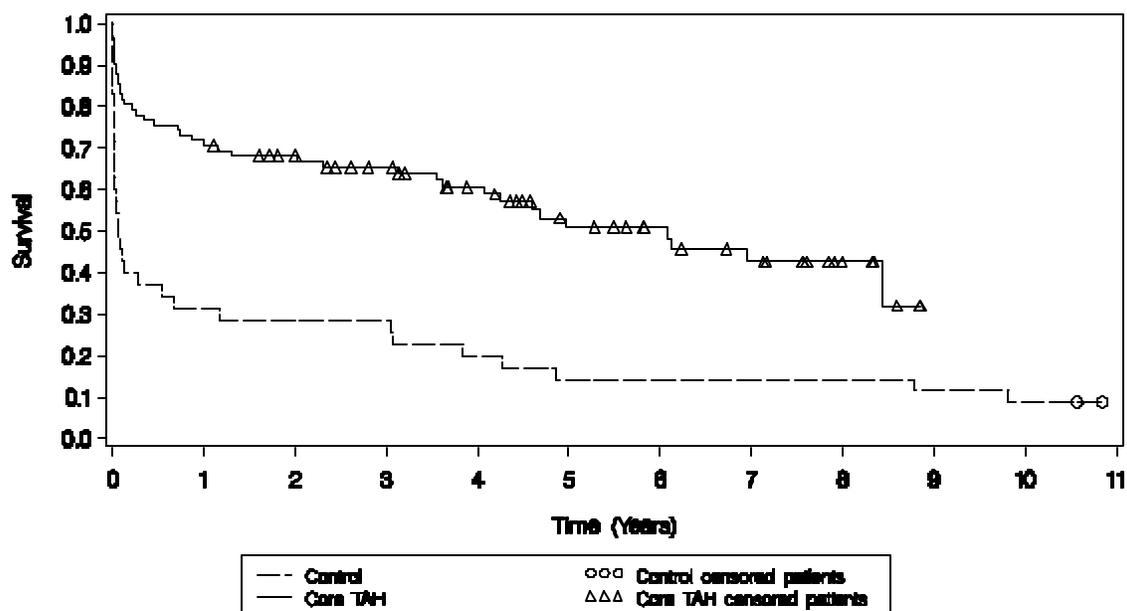
Figure 1 graphically shows that all control patients were either transplanted within 6 weeks of study entry or died while waiting for a donor heart. The curve dramatically demonstrates the difference between the core and control groups in terms of their duration of survival to transplant or death.

**Figure 1 – Kaplan-Meier Estimate of Duration of Survival to Transplant or Death (Control and Core Patients)**



Significant reduction in overall mortality occurred in core patients implanted with the device awaiting transplant compared to control patients who did not receive an implant. All patients in this study reached at least the 2 year post transplant interval and at 2 years the comparative survival was 29% (controls) vs. 68% (core).

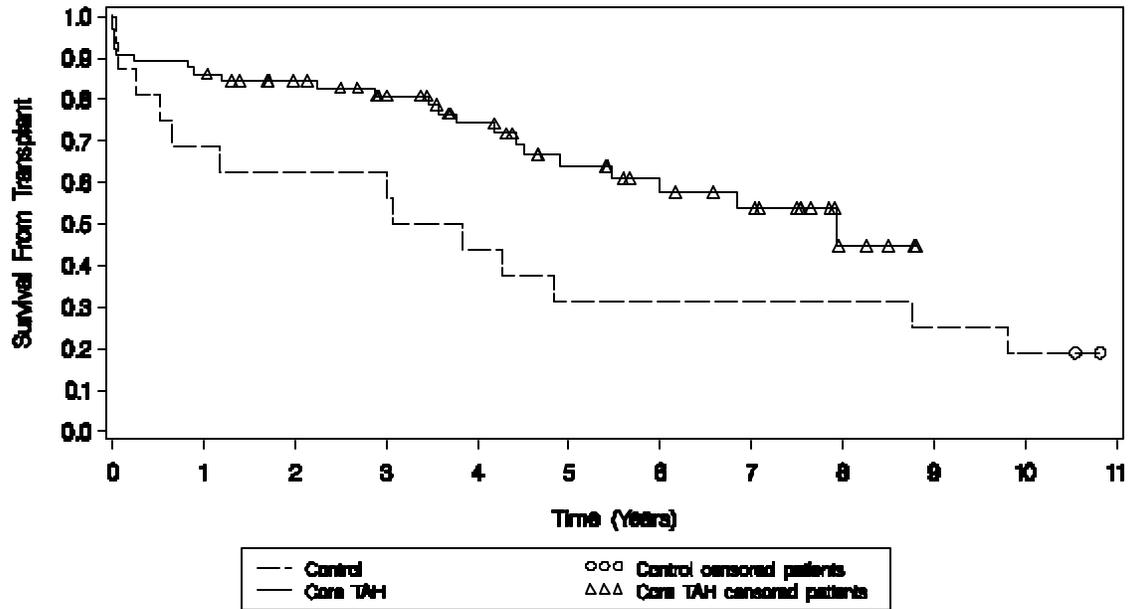
**Figure 2 – Kaplan-Meier Estimate of Overall Duration of Survival (Control and Core Patients)**



Time (years)								
	0.5	1	2	3	4	5	6	7
<b>Control (n=35)</b>								
Survival rate (%)	37.1	31.4	28.6	28.6	20.0	14.3	14.3	14.3
Standard error (%)	8.2	7.8	7.6	7.6	6.8	5.9	5.9	5.9
n	13	11	10	10	7	5	5	5
<b>Core (n=81)</b>								
Survival rate (%)	75.3	70.4	67.9	65.1	60.4	50.8	50.8	42.4
Standard error (%)	4.8	5.1	5.2	5.3	5.6	6.2	6.2	6.8
n	61	57	51	44	35	24	19	14
Log rank test P-value	<0.0001							

Survival post transplant was comparable between the core and control groups. Therefore, improvement in overall survival for the implanted patients was a direct result of the reduced mortality during the time period that they were on the device pending the receipt of a donor heart.

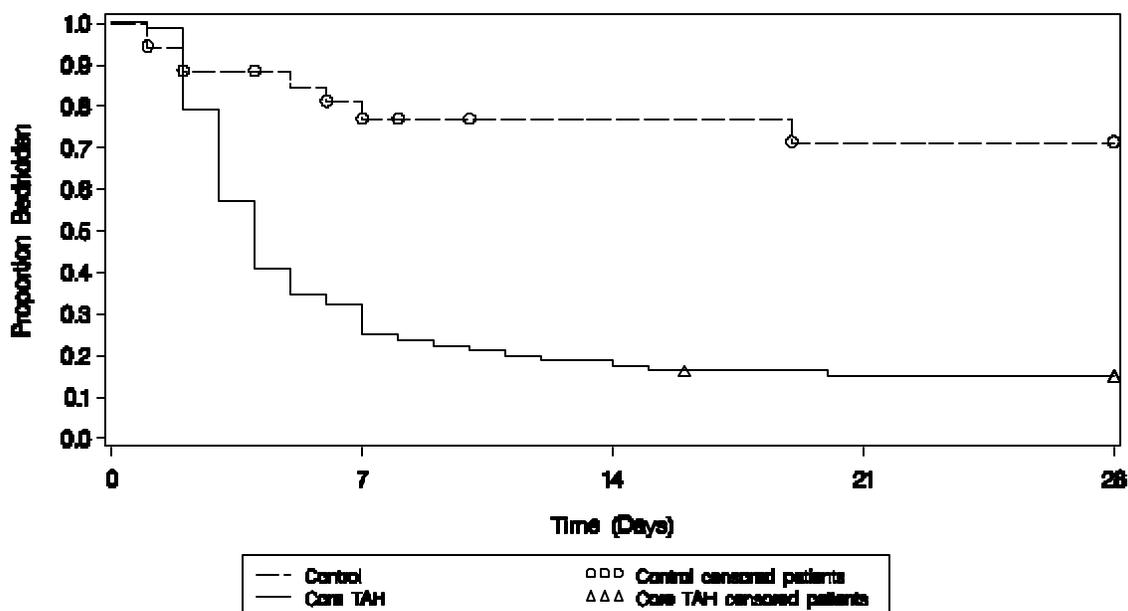
**Figure 3 – Kaplan-Meier Estimate of Duration of Survival from Transplant (Control and Core Patients)**



Time (years)								
	0.5	1	2	3	4	5	6	7
<b>Control (n=16)</b>								
Survival rate (%)	81.3	68.8	62.5	62.5	43.8	31.3	31.3	31.3
Standard error (%)	9.8	11.6	12.1	12.1	12.4	11.6	11.6	11.6
n	13	11	10	10	7	5	5	5
<b>Core (n=64)</b>								
Survival rate (%)	89.1	85.9	84.3	80.7	74.1	63.8	57.4	53.5
Standard error (%)	3.9	4.3	4.5	5.0	5.9	7.0	7.6	8.0
n	57	55	48	41	32	23	17	14
Log rank test P-value	0.0540							

The core TAH patients' ability to get out of bed and ability to walk over 100 feet was significantly improved as compared to the controls. Approximately 65% of the core patients were out of bed by the 5<sup>th</sup> day after implant, compared to 15% of controls. Two weeks after implant, 60% of core patients were walking over 100 feet, whereas in the same time period only 9% of the control patients were walking over 100 feet.

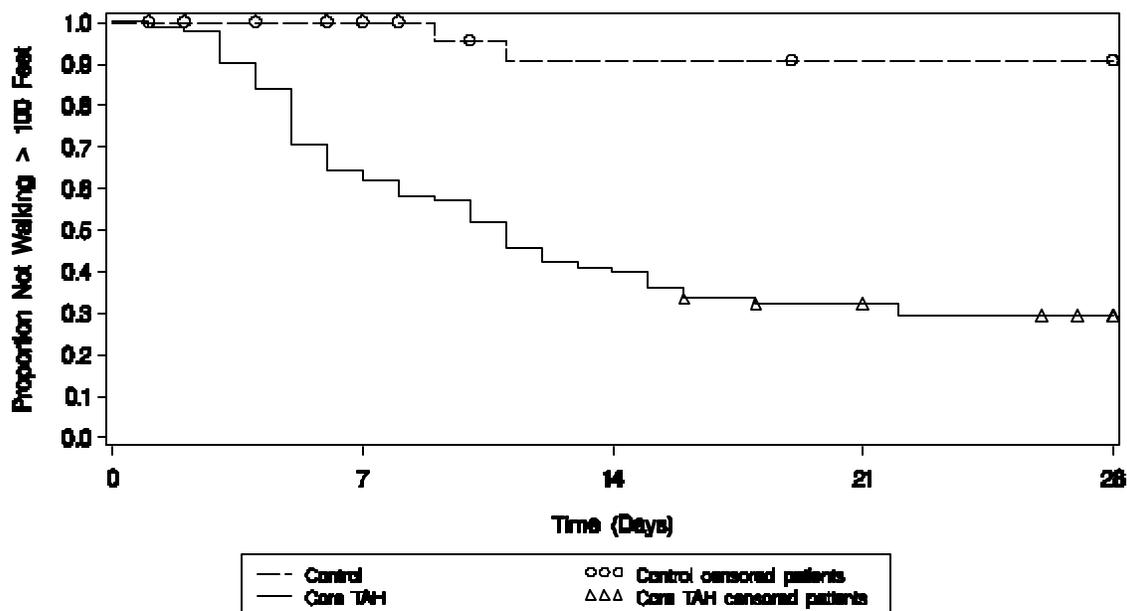
**Figure 4 – Kaplan-Meier Estimate of Time to First Getting Out of Bed (Control and Core Patients)**



Time (days)								
	1	2	3	5	7	14	21	28
<b>Control (n=35)</b>								
% not walking	94.3	88.4	88.4	84.7	76.8	76.8	71.3	71.3
Standard error (%)	3.9	5.5	5.5	6.4	7.9	7.9	9.0	9.0
n	33	30	26	23	18	14	12	12
<b>Core (n=81)</b>								
% not walking	98.8	79.0	56.8	34.6	24.7	17.3	14.7	14.7
Standard error (%)	1.2	4.5	5.5	5.3	4.8	4.2	4.0	4.0
n	80	64	46	28	20	14	11	11
Log rank test P-value	<0.0001							

Note: Time to getting out of bed is the number of days from enrollment/implant to first getting out of bed or transplant. Patients who die before getting out of bed are censored at 9999 days; patients transplanted before getting out of bed are censored at day of transplant.

**Figure 5 – Kaplan-Meier Estimate of Time to First Walking > 100 Feet (Control and Core Patients)**



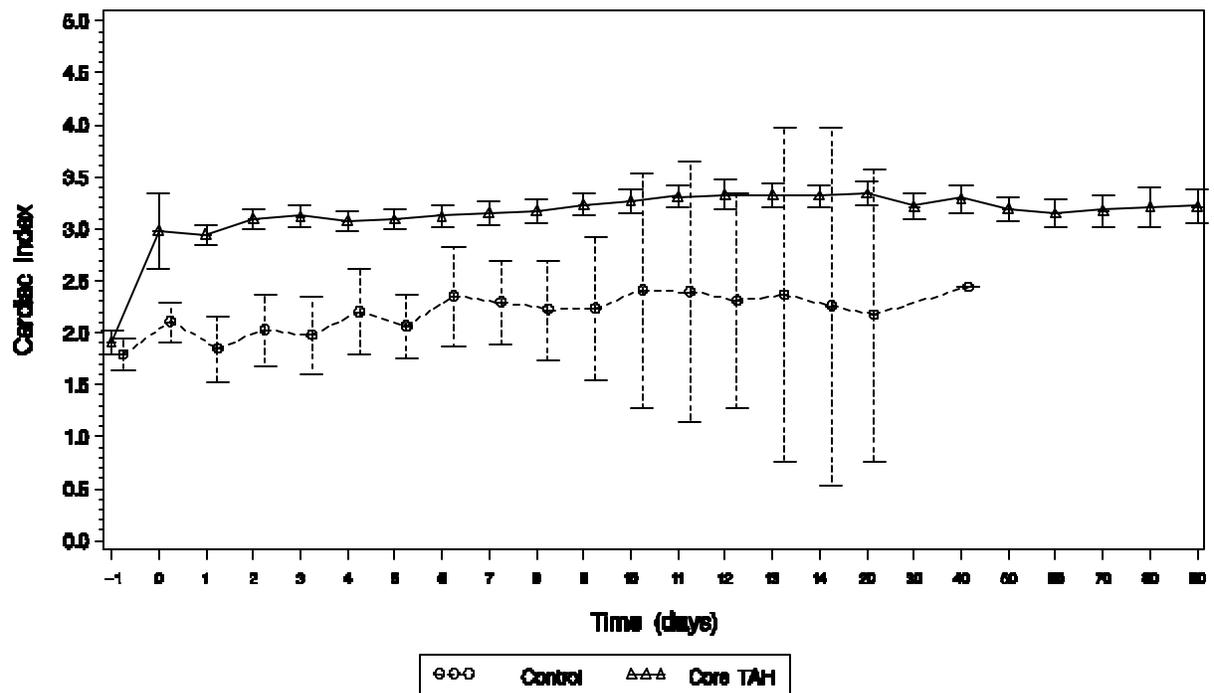
Time (days)								
	1	2	3	5	7	14	21	28
<b>Control (n=35)</b>								
% not walking > 100 ft	100.0	100.0	100.0	100.0	100.0	90.7	90.7	90.7
Standard error (%)	0.0	0.0	0.0	0.0	0.0	6.3	6.3	6.3
n	34	30	30	28	24	19	18	18
<b>Core (n=81)</b>								
% not walking > 100 ft	98.8	97.5	90.1	70.4	61.7	39.5	32.1	29.3
Standard error (%)	1.2	1.7	3.3	5.1	5.4	5.4	5.2	5.1
n	80	79	73	57	50	32	23	19
Log rank test P-value	<0.0001							

**Note:** Time to walking > 100 ft is the number of days from enrollment/implant to first walking > 100 ft or transplant. Patients who die before walking > 100 ft are censored at 9999 days; patient transplanted before walking > 100 ft are censored at the day of transplant.

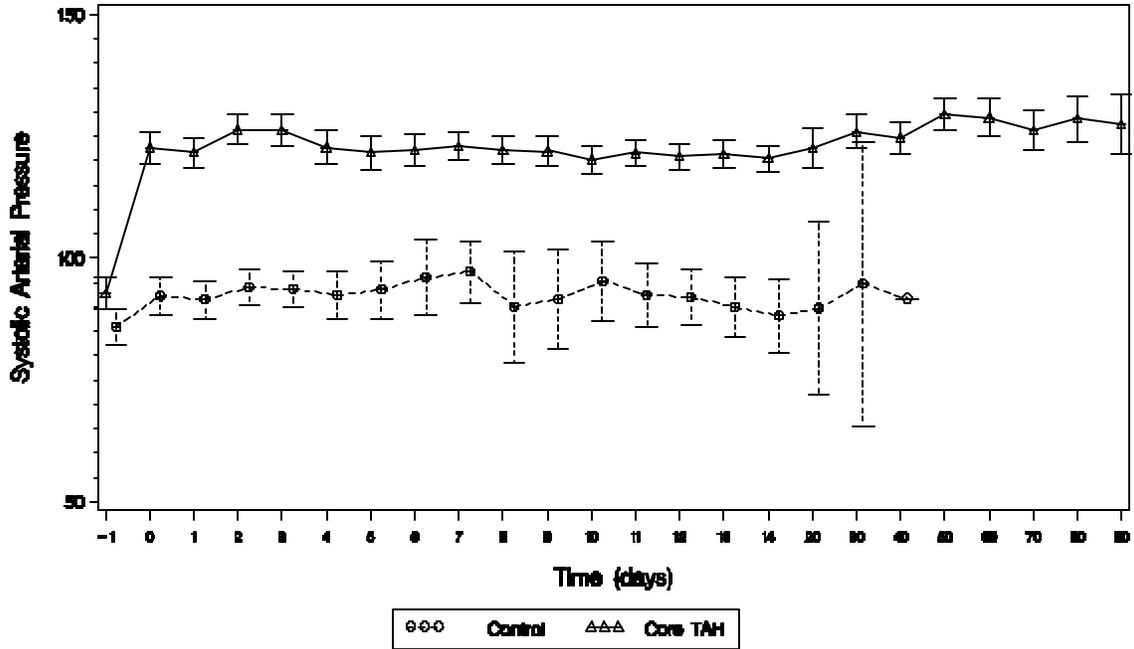
Core patients had an immediate and sustained improvement in their hemodynamic variables while on the TAH awaiting transplantation. Cardiac index improved from 1.9 L/min/m<sup>2</sup> to 3.0 L/min/m<sup>2</sup> immediately after implant, a 58% improvement, with sustained levels throughout the implant period. Systolic blood pressure increased from a baseline 92.8 mm Hg to 122.7 mm Hg, a 32% improvement, immediately following transplant, and was also sustained through the implant period.

Organ perfusion pressure (transcapillary or whole body perfusion pressure) increased by 42% immediately following implant with the TAH. An increase in perfusion pressure is a measurement of increased whole-body perfusion which leads to organ recovery. Perfusion pressure is calculated by subtracting the central venous pressure from the mean arterial pressure. Perfusion pressure was improved and maintained throughout the implant period for core implant patients.

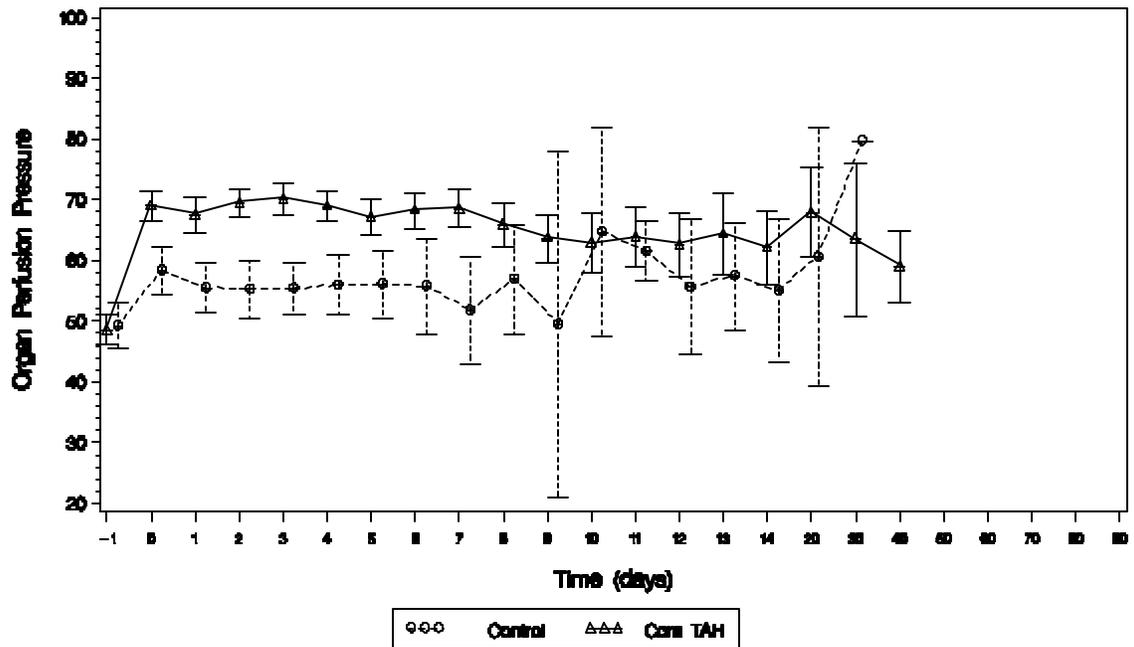
**Figure 6 – Mean (+/- 2SE) Cardiac Index by Study Period (Control and Core Patients)**



**Figure 7 – Mean (+/- 2SE) Systolic Arterial Pressure by Study Period (Control and Core Patients)**

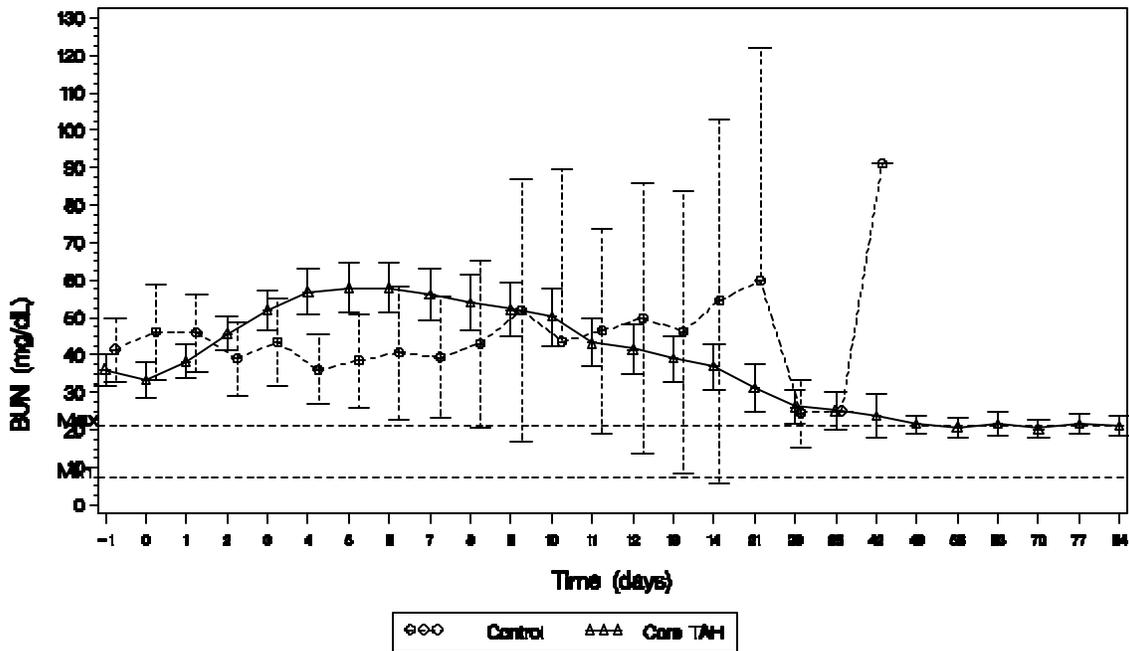


**Figure 8 – Mean (+/- 2SE) Organ Perfusion Pressure by Study Period (Control and Core Patients)**

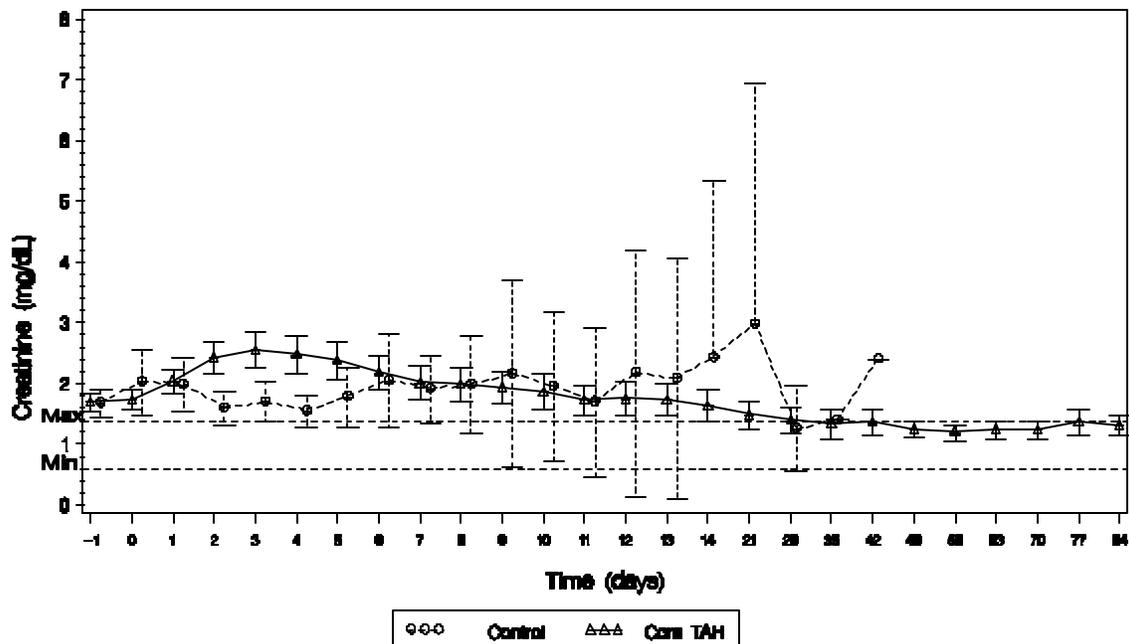


Both renal and hepatic function in the core implant population normalized after 3 weeks. At study entry the renal and hepatic functions were adversely affected by the patients' heart conditions shown by elevated blood urea nitrogen (BUN), creatinine, total bilirubin and SGOT levels above maximum normal. After the TAH implant surgery and recovery from surgery (approximately 3 weeks) the levels normalized in the core group and were often in the normal range for these markers of renal and hepatic function.

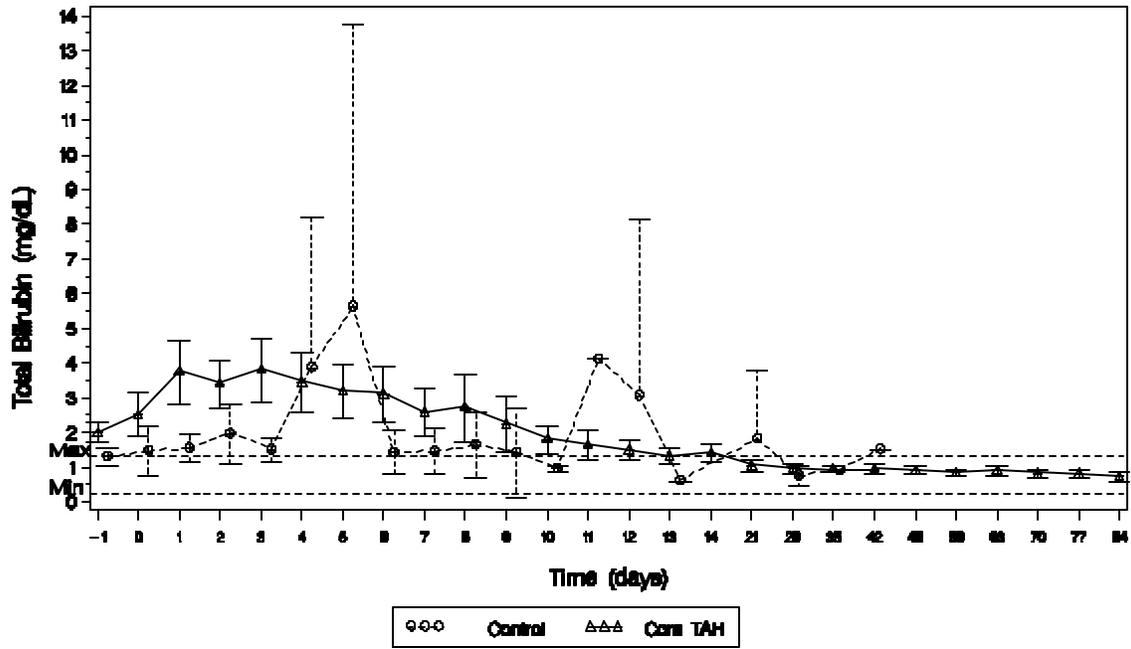
**Figure 9 – Mean (+/- 2SE) BUN by Study Period (Control and Core Patients)**



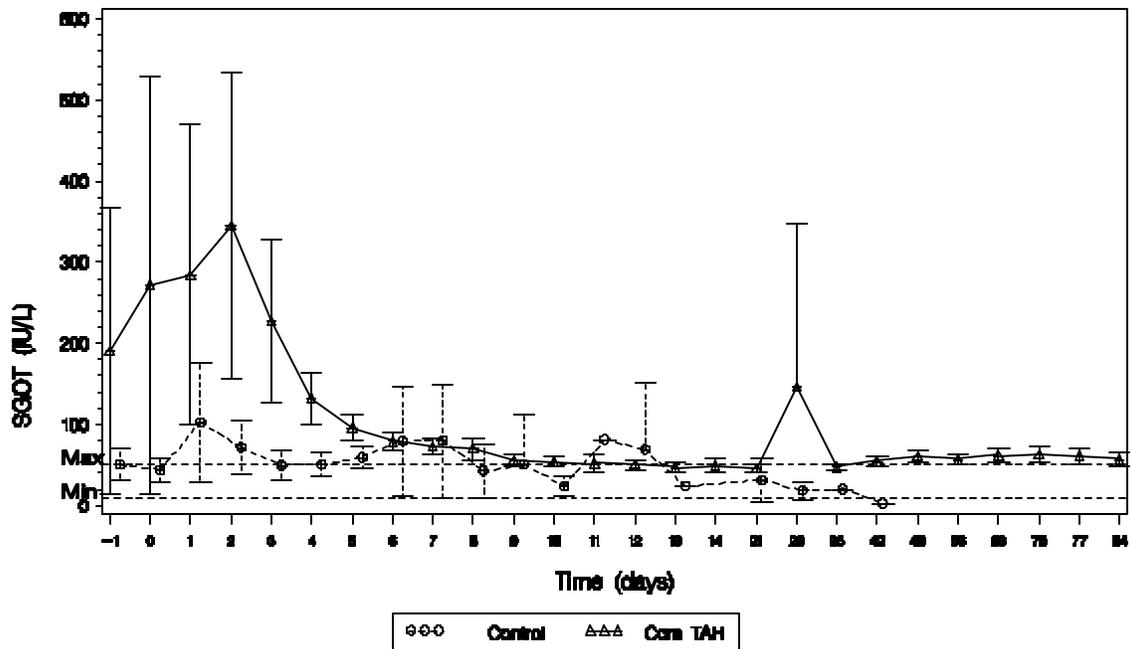
**Figure 10 – Mean (+/- 2SE) Creatinine by Study Period (Control and Core Patients)**



**Figure 11 – Mean (+/- 2SE) Total Bilirubin by Study Period (Control and Core Patients)**



**Figure 12 – Mean (+/- 2SE) SGOT by Study Period (Control and Core Patients)**



## F. Results

The primary endpoint of the study was treatment success. To be considered a success the patient must have been, at 30-days post transplantation: 1) alive; 2) NYHA Class I or II; 3) ambulatory; 4) not ventilator dependent; and 5) not on dialysis. Patients who failed these criteria were considered failures with respect to the study. At 30 days post transplant, 69.1% (56/81) of the core implant group met the criteria for treatment success, compared to only 37.1% of the control patients. The difference was highly significant at  $p=0.0019$ . Statistical significance was also found with respect to survival to transplant and survival to 30 days post transplant.

**Table 9 - Clinical Trial Outcomes - Control vs. Core**

Outcome n(%) <sup>a</sup> (95% CI)	Control Patients N=35	Core Patients N=81	p-Value
Survived to transplant	16 (45.7%) (28.8% - 63.4%)	64 (79.0%) (68.5% - 87.3%)	0.0008
Survived to 30 days post Transplant	14 (40.0%) (23.9% - 57.9%)	58 (71.6%) (60.5% - 81.1%)	0.0018
Treatment success (30 days post Transplant)	13 (37.1%) (21.5% - 55.1%)	56 (69.1%) (57.9% - 78.9%)	0.0019

Device effectiveness results establish that the SynCardia CardioWest Total Artificial Heart is effective in providing bridge to transplant circulatory support in cardiac transplant candidates at risk of imminent death from non-reversal bi-ventricular failure. The primary endpoint of treatment success was met. In addition, the clinical trial demonstrates a significant increase in survival for patients bridged on an implantable CardioWest TAH.

Secondary effectiveness parameters measured the improvement in hemodynamics, the ability to ambulate and to walk 100 feet for core patients awaiting transplant. At the time of TAH implantation, cardiac index increased to an average of 3.0 l/min/m<sup>2</sup>, an increase of 58% from baseline. Following TAH implant, systolic blood pressure increased to an average of 123 mm Hg (32% from baseline), and mean transcapillary perfusion pressure (mean blood pressure minus central venous pressure) increased to an average of 69 mm Hg, up 42% from baseline, an indication of improved organ perfusion. This near normalization of hemodynamic parameters corresponded to the ability of core patients to ambulate and walk more than 100 feet. By two weeks 71.6% of core patients (vs. 12.8% of controls) were ambulatory, and 60.5% could walk >100 feet, compared to 9.3% of control patients.

Both renal and hepatic recovery with normal laboratory parameters was evident within one month after implant of the TAH.

## XI. CONCLUSIONS

Results demonstrate that the SynCardia CardioWest Total Artificial Heart performed reliably on the bench and as intended during the clinical trial. The materials used in its composition are biocompatible with human tissue and blood. The device meets the FDA and ISO guidelines to assure sterility.

All patients enrolled in the study had the opportunity to reach at least 24 months follow-up. Outcomes are summarized in the table below.

**Table 10**  
**Summary of Outcomes**

<b>Outcome</b>	<b>Control</b>	<b>Core</b>	<b>P-value</b>
<b>Overall Survival</b>			
Survival overall at 6 months	37.1%	75.3%	<0.0001
Survival overall at 12 months	31.4%	70.4%	<0.0001
Survival overall at 24 months	28.6%	67.9%	<0.0001
<b>Survival to Transplant</b>			
Survival to transplant	45.7%	79.0%	0.0008
<b>Time to Transplant</b>			
Mean time to Transplant or death	8.5 days	79.1 days	<0.0001
<b>Eligibility for Transplant</b>			
Hepatic function normalization	never	21 days	N/A
Renal function normalization	never	28 days	N/A
Mean Organ Perfusion (day 1) increase from baseline	? 3.0 mm Hg	? 21.1 mm Hg	<0.0001
<b>Quality of Life While Awaiting Transplant</b>			
Cardiac index (day 1) increase from baseline	? 0.2 L/min/m <sup>2</sup>	? 1.1 L/min/m <sup>2</sup>	0.0352
% patients ambulatory	25.7%	86.4%	<0.0001
% patients walking 100 feet	5.7%	75.3%	<0.0001
<b>Overall Treatment Success</b>			
Alive 30-days post Tx, NYHA Class I or II, and not bedridden, ventilator dependent or on dialysis	37.1%	69.1%	0.0019

The clinical study showed that the device is effective as a bridge-to-transplantation in patients who are at imminent risk of dying from non-reversible biventricular heart failure. The data obtained in this multi-centered trial demonstrate that the CardioWest TAH is effective in improving the survival rates for transplant eligible patients waiting for donor hearts. In patients implanted with the TAH, hemodynamic status improved and renal and hepatic function returned to normal within one month. Treatment outcomes post transplant were nearly identical for the core and control patients.

The benefits offered to the patients implanted with the SynCardia TAH include the additional time to await transplant, improved hemodynamics resulting in early ambulation, and finally, an increased probability of surviving until transplant and the 30-day post operative period. These benefits outweigh the risks associated with adverse events that occurred.

## **XII. PANEL RECOMMENDATIONS**

## **XIII. CDRH DECISION**

## **XIV. APPROVAL SPECIFICATION**