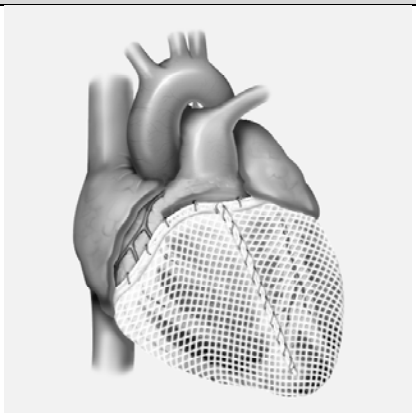
APPPENDIX E

INSTRUCTIONS FOR USE

CorCap™ Cardiac Support Device

Instructions for Use

DESCRIPTION



The CorCap™ Cardiac Support Device (CSD) is a proprietary polyester mesh wrap implanted around the heart to provide ventricular support and reduce ventricular wall stress.

INTENDED USE

The CorCap CSD is designed to provide ventricular support and reduce ventricular wall stress in patients with dilated cardiomyopathy and symptomatic heart failure. The CorCap CSD provides beneficial changes in cardiac structure as evidenced by a statistically significant reduction in left ventricular (LV) size and a significant change to a more elliptical shape. The CorCap CSD also provides a significant decrease in the need for additional major cardiac procedures associated with the progression of heart failure and a significant improvement in quality-of-life as measured by both the Minnesota Living with Heart Failure and the SF-36 questionnaires.

INDICATIONS

Patients diagnosed with dilated cardiomyopathy and symptomatic heart failure who meet the following criteria:

- Optimal heart failure medical management
- Indexed left ventricular end diastolic dimension $\geq$ 30 mm/m^2 and $\leq$ 40 mm/m^2
- LVEF $\leq$ 35% (or $\leq$ 45% if planned mitral valve repair or replacement)

CONTRAINDICATIONS

Patients with any condition considered to be a contraindication for cardiac surgery should not undergo surgery for implant of the CorCap CSD.

WARNINGS

1. Similar to any patient with a device implant, patients who receive a CorCap CSD implant are at a greater risk for development of adhesions and fibrosis. This could increase the surgical time required for subsequent cardiac surgeries, and make subsequent CABG extremely difficult or impossible.
2. Placement of device over patent coronary artery bypass grafts has not been evaluated and may compromise graft patency.
3. Do not perform procedure in patients with primary restrictive disease.
4. Do not perform procedure in patients with an active infection.

PRECAUTIONS – SPECIAL PATIENT POPULATIONS

1. The 300 patient study of the CorCap CSD involved only 30 patients with ischemic etiology since the design of the study did not allow concomitant surgical revascularization. The results from these 30 patients were not significantly different from the remaining 270 patients (p=0.42). However, this sample size was not large enough to have meaningful power to detect a difference. Patients with ischemic etiology will be specifically evaluated in a post-approval study to ensure that outcomes for these patients do not differ from the results shown in the 300 patients study.
2. The 300 patient study of the CorCap CSD involved 10 patients who received coronary endovascular therapy (i.e., angioplasty/stenting) prior to CorCap CSD implantation. One patient received a stent after CorCap CSD placement. There were no adverse events in the treatment group related to these therapies; however, safety and effectiveness of the CorCap CSD in these patients has not been established due to the limited patient population.
3. Patients with hypertrophic obstructive cardiomyopathy or primary diastolic dysfunction have not been studied in any trial and may not benefit from the CorCap CSD implant.
4. Procedure requires ability to obtain complete circumferential access to the heart, which may be compromised in patients with pre-existing pericardial or epicardial adhesions.
5. Procedure may not be possible in patients with profound cardiomegaly (>14.6 cm external cardiac diameter), which exceeds the largest CorCap CSD size available.
6. Patients who are high risk candidates for cardiac surgery (i.e., patients diagnosed with end-stage NYHA functional class IV or patients dependent upon intravenous inotropes, intra aortic balloon pump, and/or left ventricular assist device) will also be high risk candidates for CorCap CSD therapy.

PRECAUTIONS

1. If hemodynamic instability during manipulation of the heart for placement of the posterior sutures occurs and cannot be managed by pharmacological means, use of CPB or placement of IABP is recommended.
2. As with any cardiac surgery, use of an adhesion barrier may be considered, particularly in patients with an increased potential for requiring future operations.
3. Because the direct application of antibiotics to the CorCap CSD has not been adequately studied, the interaction between antibiotics and the CorCap CSD is not predictable and should be avoided.
4. Alteration to the device or implant procedure beyond these instructions may result in unknown device performance.

ADVERSE EVENTS

POTENTIAL ADVERSE EVENTS

Based on the literature review of cardiac surgery experience and clinical trial experience with the CorCap CSD, the following alphabetical list includes possible adverse events associated with implantation of the CorCap CSD:

- Allergic response
- Bleeding (internal and external)
- Cardiac arrythmias
- Cardiac tamponade
- Chronic pain
- Hemodynamic compromise potentially leading to cardiogenic shock and/or neurological deficit
- Fibrotic tissue formation (e.g., keloid formation)
- Death
- Infection, sepsis
- Myocardial infarction
- Other surgical trauma
- Pericarcial effusion
- Pericarditis
- Pneumothorax
- Pulmonary, renal, or hepatic compromise potentially leading to failure
- Reoperation
- Thromboembolism
- Tissue reaction (local)

SUMMARY OF CLINICAL STUDIES

The study *Clinical Evaluation of the Acorn Cardiac Support Device Therapy in Patients with Dilated Cardiomyopathy – A Randomized Trial in the United States and Canada* was initiated by Acorn Cardiovascular Inc., under the approved IDE G990267 in June 2000.

STUDY DESIGN OVERVIEW

This study was a 300 patient prospective, randomized, controlled, multi-center trial. Patients were randomly allocated to receive the CorCap CSD implant with or without mitral valve repair or replacement (MVR) or to the control group with or without MVR. All patients in the treatment and control groups received optimal medical therapy.

OBJECTIVES

Primary Objective: To compare patient functional status after a minimum of 12 months of follow-up for patients randomly assigned to treatment (CorCap CSD implant) or control (no CorCap CSD implant).

Secondary Objectives: 1) To determine the rate of death and other serious adverse events experienced by patients assigned to the CorCap CSD implant and to compare this rate with that for patients assigned to the control group; 2) To compare patient functional status and structural changes in the heart for the treatment and the control groups.

PRIMARY COMPOSITE ENDPOINT

The primary endpoint was a composite ordinal endpoint based on death, major cardiac procedures indicative of progression of heart failure, and change in core lab assessment of New York Heart Association (NYHA) functional classification. At the end of the study, patients assigned to the treatment group were compared to patients assigned to the control group for assessment of their functional status as follows:

Worsened-patient died, experienced a major cardiac procedure or was classified as at least one category worse on core lab NYHA as compared to baseline.
Same-patient is alive, did not experience a major cardiac procedure and was classified as the same on core lab NYHA as compared to baseline.
Improved-patient is alive, did not experience a major cardiac procedure and was classified as at least one category improved on core lab NYHA as compared to baseline.

SECONDARY EFFICACY ENDPOINTS

The following secondary endpoints were assessed compared to baseline measurement (pre-randomization):

- Change in left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV)
- Change in left ventricular ejection fraction (LVEF) as measured via echocardiography.
- Change in quality of life as determined from the Minnesota Living with Heart Failure (MLHF) and SF-36 questionnaires.
- Change in NYHA functional class as determined by the site clinician and the core lab clinician.
- Change in left ventricular end-diastolic dimension (LVEDD), left ventricular end-systolic dimension (LVESD), mitral regurgitation and sphericity as measured via echocardiography.
- Number of hospitalizations, hospital days and ICU days, cardiac related and overall.
- Change in exercise status as measured by 6-minute walk distance.
- Change in peak oxygen consumption and anaerobic threshold as measured on the cardiopulmonary exercise test (CPX).
- Change in B-type natriuretic peptide (BNP) content in blood plasma.
- All-cause mortality and re-hospitalization.
- Incidence of major cardiac procedures.

INCLUSION CRITERIA

- Dilated cardiomyopathy of either ischemic or non-ischemic origin.
- Stable and optimal medical management including all of the following:
  - √ Angiotensin-converting enzyme inhibitors (ACE) or alternate if ACE not tolerated
  - √ Diuretic at least "prn" (as occasion required)
  - √ Treatment with a beta-blocker (unless intolerant) for ≥ 3 months (not required for patients with a mitral valve anomaly that is not likely to respond to medications and requires surgical intervention)
  - √ Cardiac medications unchanged for ≥ 1 month except for diuretic adjustments (not required for patients with a mitral valve anomaly that is not likely to respond to medications and requires surgical intervention)
- Adult (18-80 years).
- Left ventricular end-diastolic dimension (LVEDD) ≥ 60 mm or LVEDD index ≥ 30 mm/m^2 as determined by transthoracic echocardiography.
- Mitral regurgitation (MR) ≤ 2+ unless scheduled for MVR.

- Signed Informed Consent.
- Left ventricular ejection fraction (LVEF) ≤ 35% via transthoracic echocardiography, cardiac catheterization, radionuclide scan or magnetic resonance imaging or LVEF ≤ 45% and planned MVR.
- New York Heart Association Functional Class (NYHA) III or IV or NYHA II if scheduled MVR.
- Baseline 6-minute walk distance < 450 meters (1476 feet).
- Acceptable hepatic function with serum glutamic oxalo-acetic transaminase (SGOT or AST) and serum glutamic pyruvic transaminase (SGPT or ALT) < 3X upper limit of normal.
- Acceptable pulmonary function as assessed clinically unless there is history of compromise or current evidence of compromise, in which case forced expiratory volume in the first second (FEV1) must be > 50% of predicted normal value.
- Geographically available for follow-up.

EXCLUSION CRITERIA

- Planned cardiac surgical procedure other than MVR with or without tricuspid valve repair or atrial fibrillation ablation procedure.
- Hypertrophic obstructive cardiomyopathy.
- Significant cardiomegaly, estimated to exceed the largest available device size.
- Existing cardiothoracic adhesions that would preclude cardiac circumferential access.
- Any condition considered a contraindication for extracorporeal circulation.
- Late-stage heart failure with increased surgical risk as defined by the presence of **four** or more of the following:
  - √ LVEDD ≥ 80 mm
  - √ Peak VO_2 ≤ 13 ml/kg/min (cardiopulmonary exercise test)
  - √ Resting systolic BP ≤ 80 mmHg (on clinical exam)
  - √ Atrial fibrillation at time of enrollment or paced rhythm with underlying atrial fibrillation
  - √ Heart failure duration ≥ 8 years
  - √ Exercise-induced increase in systolic BP ≤ 10% (cardiopulmonary exercise test)
  - √ 6-minute walk ≤ 350 meters (1148 feet)
  - √ Previous cardiac surgery
  - √ BUN ≥ 100 mg/dl
  - √ Cachexia (clinical impression)
- Existing patent CABG.
- Candidates for surgical revascularization as determined by an angiogram.
- Receiving an IABP, intravenous inotropic or vasoactive agents, except for immediate pre-operative hemodynamic optimization.
- Current or anticipated need for LVAD or cardiac replacement device.
- On active transplant list or anticipated need for heart transplant within the next two years.
- Acute myocardial infarction, unstable angina or cerebral vascular accident (TIA or CVA) within the past 3 months.
- Percutaneous coronary intervention or transmyocardial laser revascularization (TMR or PMR) within the past 3 months.
- Presence of arrhythmias causing hemodynamic instability, history of resuscitated sudden death without subsequent treatment with implantable defibrillator or amiodarone or atrial fibrillation with a ventricular rate > 100 bpm on medication.
- Co-morbid condition that reduces life expectancy to less than 1 year.
- Serum creatinine ≥ 3.5 mg/dl or dialysis dependent.
- Bi-ventricular (BiV) pacing initiated within the past 3 months or anticipated within the next 12 months.

- Active infection.
- Pregnancy at the time of enrollment. (Women of child bearing potential must have a negative serum pregnancy test within two weeks prior to randomization, or must be using hormonal contraceptives or intrauterine devices.)
- Enrolled in another investigational study that would confound interpretation of trial results, or receiving experimental or investigational drugs.
- Unable to comply with protocol-required follow-up (as judged by primary investigator or referring cardiologist).

PATIENT ASSESSMENT

Pre-enrollment and follow-up testing is summarized in **Table 1.**

Table 1: Pre-enrollment and Follow-up Testing

Test	Pre-enrollment	3 Months	6 Months	12 Months & every 6 Months thereafter
Clinical Assessment	X	X	X	X
Core Lab NYHA Assessment	X		X	X
Chest X-ray	X (within past 3 months)			
Blood Tests	X	X	X	X
BNP	X	X	X	X
Echocardiography (transthoracic)	X	X	X	X
ECG	X (within past 3 months)	X	X	X (Stop after 12 months)
Cardiopulmonary Exercise Test	X (within past 3 months)		X	X (Stop after 12 months)
Six Minute Walk	X	X	X	X
MLHF and SF-36 Questionnaires	X	X	X	X
Right and/or Left Heart Catheterization	X*			
*As required for patients with ischemic heart disease.				

INVESTIGATIONAL SITES

Each site had two principal investigators; one surgeon and one cardiologist. Twenty-nine sites enrolled a total of 300 patients.

RESULTS IN RANDOMIZED TRIAL COHORT (N=300)

BASELINE CHARACTERISTICS

Table 2 summarizes the gender, age, race, and heart failure etiology at baseline. Etiologies classified as "other" included adriamycin, post partum, familial, chemotherapy, radiation,

dietary, HIV related, myocarditis, chemical exposure, peripartum, and hyperthyroid induced heart disease.

Table 2: Age, Gender, Race and Etiology at Baseline

	# Pts	Mean or %
Age (mean years)	300	52.5 years
Gender		
Male	166	55.3%
Female	134	44.7%
Race		
White	195	65.0%
Black	81	27.0%
Other	24	8.0%
Etiology		
Ischemic	30	10.0%
Idiopathic	184	61.3%
Viral	25	8.3%
Alcoholic	6	2.0%
Valvular	34	11.3%
Hypertensive	30	10.0%
Other	25	8.3%
Years Since Heart Failure Diagnosis	300	5.0 years

Table 3 summarizes the cardiac medications at baseline for all patients. A total of 97% of all patients were on an ACE Inhibitor or Angiotensin II Blocker and 85% of all patients were on a beta-blocker at the time of enrollment.

Table 3: Baseline Cardiac Medications

	# Patients	% of 300
ACE or A II Blocker	291	97.0%
ACE Inhibitor	236	78.7%
Angiotensin II (A II) Blocker	70	23.3%
Beta Blocker	256	85.3%
Diuretic	294	98.0%

PRIMARY COMPOSITE ENDPOINT

The analysis of the primary composite endpoint placed patients into one of three categories: improved, same, or worsened (**Table 4**). Patients were placed in the "worsened" category if any one of three endpoints was reached: if the patient died, if the patient had a major cardiac procedure indicative of progressive heart failure or if the patient's core lab NYHA status deteriorated by one or more NYHA class when compared from baseline to last follow-up visit. In order to qualify for the primary endpoint, major cardiac procedures had to be adjudicated by the Clinical Events Review Committee (CERC) as being associated with clear evidence of worsening heart failure. Patients were classified in the "same" category if they did not die, did not have a major cardiac procedure and the NYHA class was the same at baseline and last follow-up. Patients were classified as "improved" if they did not die, did not have a major cardiac procedure and the NYHA class had improved by one or more class from baseline to last follow-up.

Table 4: Description of Primary Endpoint

Patient Classification	Any One of			Same NYHA	Improved NYHA
	Death	MCP*	Worsened NYHA		
Improved	Ø	Ø	Ø	Ø	☑
Same	Ø	Ø	Ø	☑	Ø
Worsened	☑	☑	☑	Ø	Ø

*Adjudicated major cardiac procedures indicative of worsening heart failure: transplant, LVAD, CABG, bi-ventricular pacing and MVR.

Table 5 summarizes the primary composite endpoint results. The CorCap CSD treatment group had a greater frequency of improvement (37.7% versus 27.3%). In addition, the treatment group had a lower frequency of worsening (37.2% versus 45.1%) when compared to the control group. Proportional odds analysis of this distribution yielded an odds ratio of 1.73 (95% CI: 1.07, 2.79). This odds ratio of the primary endpoint was statistically significant at p=0.024, and indicated that the treatment group had 73% better odds of being in a better category when compared to the control group.

Table 5: Primary Composite Endpoint

	Treatment (Average %)	Control (Average %)	Odds Ratio T/C (95% CI)	p-value
Improved	37.7	27.3	1.73 (1.07, 2.79)	**0.024**
Same	25.1	27.7		
Worsened	37.2	45.1		

COMPONENTS OF PRIMARY ENDPOINT

MORTALITY

Figure 1 provides the Kaplan-Meier curve for mortality as of December 30, 2005. There were 38 deaths in control and 32 deaths in treatment (p=0.52). These data indicate that there was no excess mortality risk in the treatment group.

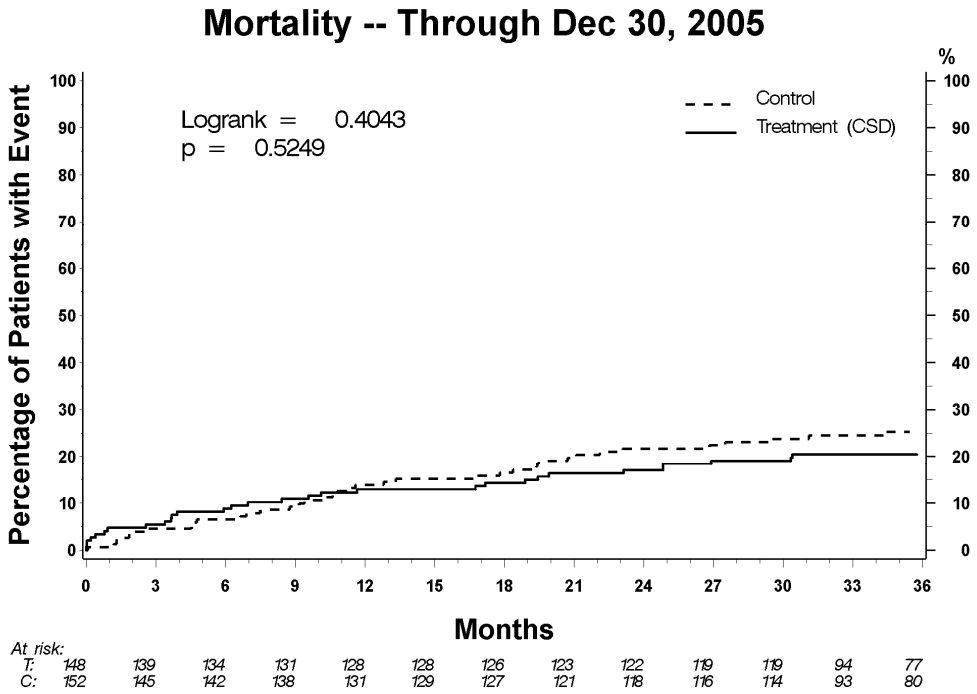
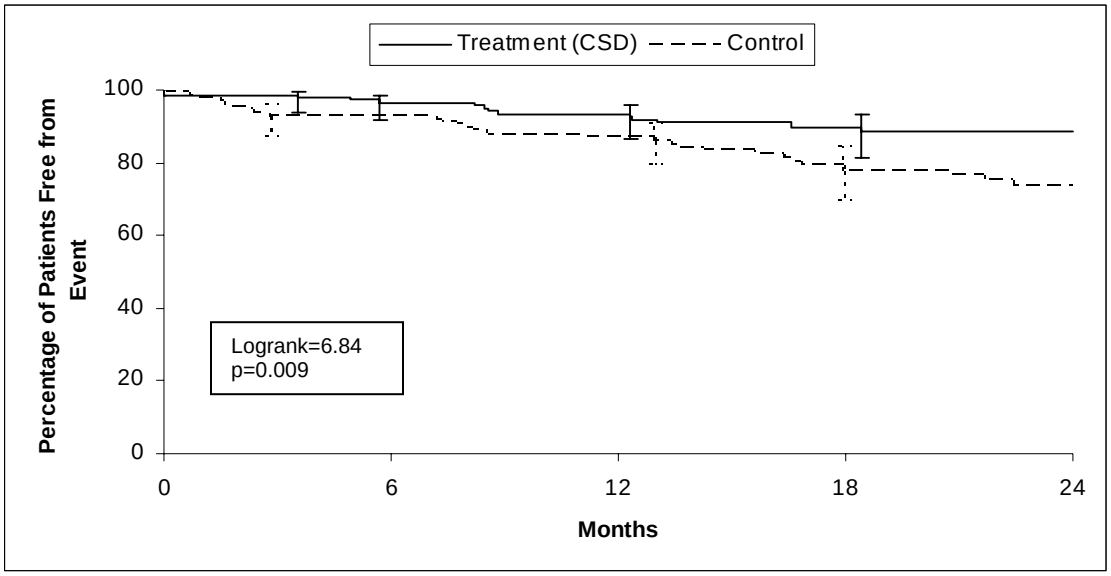


Figure 1: Mortality

MAJOR CARDIAC PROCEDURES

Figure 2 illustrates the Kaplan-Meier curve for the endpoint of freedom from major cardiac procedure. The curves separated early and continued to separate throughout the follow-up period. The cumulative percent of patients free from a major cardiac procedure indicative of worsening heart failure was significantly higher in the treatment group through 24 months (p=0.009). In addition, the major cardiac procedures in the control group occurred throughout the follow-up period, consistent with the development of worsening heart failure. This indicates that the CorCap CSD significantly reduces the need for additional major cardiac procedures.



At risk	BL	6 Mo	12 Mo	18 Mo	24 Mo
T:	148	129	120	75	52
C:	152	130	114	69	36

Figure 2: Freedom from Major Cardiac Procedure

CHANGE IN NYHA CLASS

The third component of the primary endpoint was functional status as assessed by NYHA classification, assessed by a central core laboratory. At final follow-up, outcomes were better in the CorCap group than in the control, but the difference was not statistically significant (**Table 6)**. Note that subjects who had died or had undergone a major cardiac procedure were censored from the analysis.

Table 6: NYHA Component of the Primary Composite Endpoint

	Treatment (Average %)	Control (Average %)	Odds Ratio T/C (95% CI)	p-value
Improved	52.3	42.8	1.64	0.12
Same	34.8	43.4		
Worsened	13.0	13.8		

OBSERVED ADVERSE EVENTS

Table 7 and **Table 8** summarize serious adverse events in the No MVR and MVR strata broken down into the early phase and the late phase using data available in the pivotal study cohort thorough 15 April 2005. The major difference between the treatment and control groups in the No MVR stratum was found in the early stage. Since the treatment group undergoes implant surgery, they experienced a significantly greater rate of adverse events within 30 days of surgery related to hemodynamic compromise (p=0.007), pulmonary compromise (p=0.01) and infection (p=0.03). However, after this initial phase, there was no excess of AEs in the treatment group. In the MVR stratum, both the treatment and control groups undergo surgery. There were no differences between the treatment and control groups in the rate of serious adverse events either in the early or late periods in the MVR stratum.

Table 7: Incidence of SAEs by Time Period - No MVR Stratum

	≤ 30 Days						> 30 Days					
	Treatment		Control				Treatment		Control			
Event	Events	Rate	Events	Rate	HR (T/C)	p-value	Events	Rate	Events	Rate	HR (T/C)	p-value
Hemo Compromise	18	44.5	5	10.8	3.93	0.007	23	2.1	24	2.7	0.75	0.32
Pulmonary Compromise	7	15.0	0	0.0	NA	0.01	1	0.1	3	0.2	NA	0.34
Neurologic Event	1	2.0	0	0.0	NA	1.00	1	0.1	5	0.4	0.19	0.12
Infection/ Pneumonia	6	12.5	0	0.0	NA	0.03	8	0.6	8	0.6	0.94	0.90
Any SAE or Death	31	97.9	7	15.2	5.48	<0.001	40	5.3	38	6.1	0.82	0.38
Patients at risk	57		50				51		50			

Table 8: Serious Adverse Events – MVR Stratum

	≤ 30 Days						> 30 Days					
	Treatment		Control				Treatment		Control			
Event	Events	Rate	Events	Rate	HR (T/C)	p-value	Events	Rate	Events	Rate	HR (T/C)	p-value
Hemo Compromise	21	28.7	24	29.3	1.02	0.95	46	2.6	36	1.8	1.45	0.10
Pulmonary Compromise	17	22.0	12	13.4	1.64	0.19	11	0.5	11	0.4	1.07	0.87
Neurologic Event	5	5.9	2	2.0	2.76	0.23	8	0.3	5	0.2	1.78	0.31
Infection/ Pneumonia	18	23.1	13	14.5	1.55	0.23	21	0.9	20	0.8	1.19	0.57
Any SAE or Death	51	104.8	54	94.5	1.07	0.74	63	4.6	70	5.3	0.93	0.68
Patients at risk	91		102				88		101			

RESULTS IN FOCUSED COHORT

In collaboration with FDA, Acorn analyzed the 300-patient PMA cohort for the CorCap CSD to determine the patient population with the greatest benefit-risk ratio. Using cumulative trends analysis, Acorn determined that patients with an indexed LVEDDi $\geq$ 30 mm/m^2 and $\leq$ 40 mm/m^2 demonstrated the largest and most consistent treatment vs control difference across all outcomes and, hence, the greatest benefit-risk profile for the CorCap CSD. Thus, patients with an LVEDDi between 30 and 40 mm/m^2 represent a ***focused cohort*** in which safety and efficacy were enhanced. This cohort consists of 159 patients from the original 300 patients (53%). The next analyses focus exclusively on these 159 patients.

BASELINE CHARACTERISTICS – FOCUSED COHORT

Table 9 summarizes the age, gender, race and heart failure etiology of the focused cohort. Patients had a mean age of 52.7 years. The percentage of females was 42% and the percentage of non-Caucasian patients was 34%. The most common etiology of heart failure was idiopathic cardiomyopathy (63%). The mean duration of heart failure was 4.9 years. Importantly, all of these baseline characteristics were similar to the original 300 patient cohort.

Table 9: Age, Gender, Race and Etiology at Baseline – Focused Cohort

	# Pts	Mean or %
Age (mean years)	159	52.7 years
Gender		
Male	92	57.9
Female	67	42.1
Race		
White	105	66.0
Black	44	27.7
Other	10	6.3
Etiology		
Ischemic	16	10.1
Idiopathic	100	62.9
Viral	13	8.2
Alcoholic	4	2.5
Valvular	16	10.1
Hypertensive	18	11.3
Other	11	6.9
Years Since Heart Failure Diagnosis	159	4.9 years

Table 10 summarizes the cardiac medications at baseline for all patients. A total of 97.5% of patients were on an ACE inhibitor or angiotensin II blocker and 86% of all patients were on a beta blocker. These percentages were similar to the original 300 patient cohort.

Table 10: Baseline Cardiac Medications – Focused Cohort

	# Patients	% of 300
ACE or A II Blocker	155	97.5
ACE Inhibitor	123	77.4
Angiotensin II (A II) Blocker	36	22.6
Beta Blocker	136	85.5
Diuretic	156	98.1

PRIMARY COMPOSITE ENDPOINT – FOCUSED COHORT

Table 11 summarizes the primary composite endpoint results in the focused cohort. The CorCap CSD treatment group had a greater frequency of improved when compared to the control group (42.5% versus 26.6%). In addition, the treatment group had a lower frequency of worsened when compared to the control group (37.9% versus 49.9%). Proportional odds analysis of this distribution yielded an odds ratio of 2.45 (95% CI: 1.23, 4.87). This odds ratio of the primary endpoint was statistically significant at p=0.011, and indicated that the treatment group had 145% better odds of being in a better category when compared to the control group.

Table 11: Primary Composite Endpoint
Focused Cohort n=159

	Treatment (Average %)	Control (Average %)	Odds Ratio T/C (95% CI)	p-value
Improved	42.5	26.6	2.45 (1.23, 4.87)	**0.011**
Same	19.7	23.5		
Worsened	37.9	49.9		

Discussion
The odds ratio and p-value from the primary endpoint analysis in the focused cohort represent an improvement from the results in the 300 patient cohort (i.e., OR=1.73; p=0.024), consistent with the intent of the focused cohort analysis to find the patient group with an enhanced safety and efficacy profile.

COMPONENTS OF PRIMARY COMPOSITE ENDPOINT – FOCUSED COHORT

MORTALITY

Figure 3 provides the Kaplan-Meier curve for mortality using data available through 15 April 2005. Overall, there were 34 deaths, including 21 of 82 patients in the control group (25.6%) and only 13 deaths among 77 patients in the treatment group (16.9%). This is an overall 34% reduction in mortality due to the CorCap CSD treatment. The Kaplan-Meier curves separated early and maintained this separation throughout the trial (p=0.17). When compared to the Kaplan-Meier curve from the original 300 patient cohort (p=0.59, as of 15 April 2005), the curves now more clearly favor the treatment group.

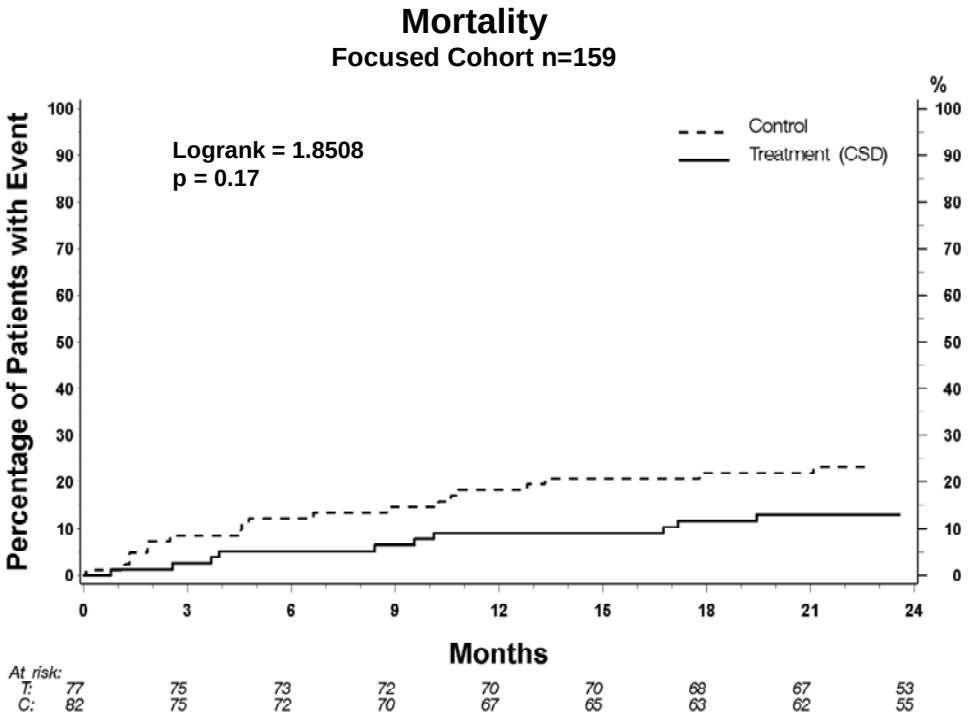


Figure 3: Kaplan-Meier Curve -- All Cause Mortality

Discussion

The results of survival in this new patient subgroup are, as expected, different from the original report. Because the LVEDDi inclusion criterion excludes patients with the highest operative and overall mortality risk, the new focused cohort shows a reduction in both operative and overall mortality risk. Therefore, instead of 7 deaths in the first 30 days for treatment patients (7/148 = 4.7%), now there is only 1 death among 77 patients (1.3%). Further, the KM survival curve shows a trend for the CorCap CSD treatment group to have a lower mortality over the follow up period. The new p-value is 0.17, favoring treatment, compared to 0.59 in the original 300 patient cohort.

MAJOR CARDIAC PROCEDURES – FOCUSED COHORT

Figure 4 illustrates the Kaplan-Meier curve for the time to major cardiac procedures. The curves separate early and continue to separate throughout the follow up period. The control group required more cardiac procedures throughout the follow up period (p=0.013).

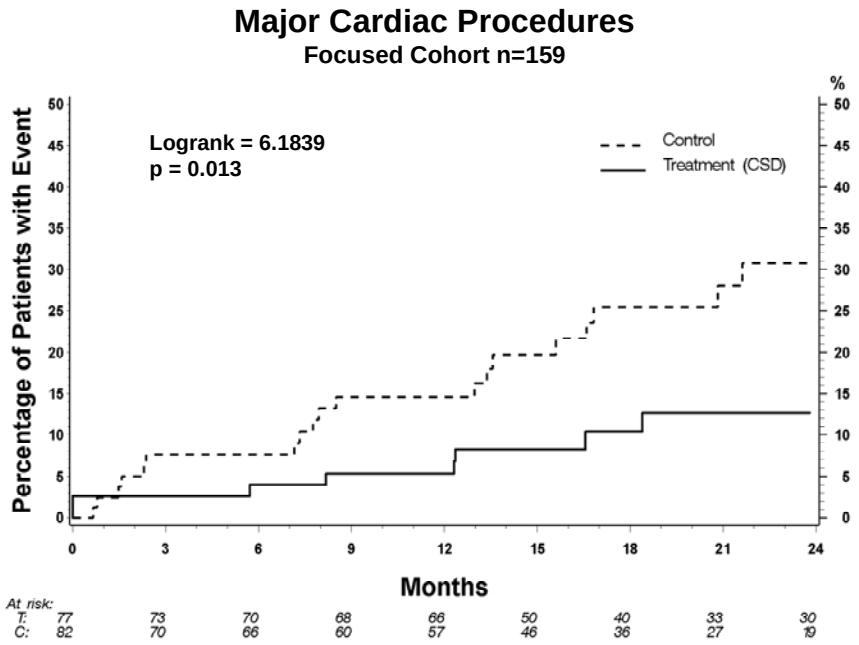


Figure 4: Major Cardiac Procedures

Discussion

This analysis demonstrated that CorCap CSD implantation significantly decreased the need for major cardiac procedures that were indicated because of worsening heart failure. This benefit is similar to what was reported in the original PMA, suggesting that the focused cohort has maintained this benefit of reduced major cardiac procedures.

CHANGE IN CORE LAB NYHA CLASS – FOCUSED COHORT

The third component of the composite clinical endpoint was the change in Core Lab NYHA (
Table 12).

The treatment group had a greater frequency of improvement by at least one NYHA class (48.8% versus 34.6%) when compared to the control group. The treatment group also had a lower frequency remaining the same (29.1% versus 48.5 %) and a slightly higher frequency of worsening (22.1% versus 16.9%) compared to the control group. This odds ratio of 1.71 (95% CI; 0.78, 3.73) favored treatment (p=0.18), and was very similar to the odds ratio of 1.74 in the 300 patient cohort.

Table 12: Change in Core NYHA
Focused Cohort n=159

	Treatment (%) n=67	Control (%) n=62	OR	p-value
Improved	48.8	34.6	1.71 (0.78, 3.73)	0.18
Same	29.1	48.5		
Worsened	22.1	16.9		

ADVERSE EVENTS

Table 13 and **Table 14** summarize serious adverse events in the No MVR and MVR strata broken down into the early phase and the late phase using data available thorough 15 April 2005. In the No MVR stratum the treatment group had more adverse events than the control group in the early phase since the treatment received implant surgery while the control group did not. However, the expected increase in the focused cohort was not as marked as in the 300 patient cohort. This attenuation of the risk profile is related to the fact that the LVEDDi criterion excludes the high risk patients who also experience many of the adverse events. In the late phase, the rate of SAE's was significantly lower in the treatment group compared to the control group (p=0.019). There were no differences between the MVR stratum groups in the rate of serious adverse events in the early or late post-op periods. This is consistent with the concept that the addition of CorCap to standard MV surgery adds very little incremental risk.

Table 13: Incidence of Serious Adverse Events by Time Period
Focused Cohort No MVR Stratum n=56

	≤ 30 Days						> 30 Days					
	Treatment		Control				Treatment		Control			
Event	Events	Rate	Events	Rate	HR (T/C)	p-value	Events	Rate	Events	Rate	HR (T/C)	p-value
Hemo Compromise	5	19.2	5	22.9	0.78	0.70	13	2.0	14	3.8	0.44	0.051
Pulmonary Compromise	4	14.5	0	0.0	-	0.12	1	0.1	2	0.3		0.58
Renal Compromise	2	6.9	0	0.0	-	0.50	1	0.1	2	0.3	0.32	0.35
Infection/Pneumonia	4	14.7	0	0.0	-	0.12	4	0.5	5	0.8	0.52	0.34
Any SAE or Death	14	76.6	7	32.5	1.98	0.15	23	4.7	20	7.0	0.46	0.019
Patients at risk	31		25				30		25			

Table 14: Incidence of Serious Adverse Events by Time Period
Focused Cohort MVR Stratum n=103

	≤ 30 Days						> 30 Days					
	Treatment		Control				Treatment		Control			
Event	Events	Rate	Events	Rate	HR (T/C)	p-value	Events	Rate	Events	Rate	HR (T/C)	p-value
Hemo Compromise	11	29.4	14	31.5	0.99	0.99	26	3.0	18	1.6	1.78	0.062
Pulmonary Compromise	9	23.1	6	12.0	1.88	0.23	4	0.3	4	0.3	1.23	0.77
Renal Compromise	2	4.6	1	1.8	2.15	0.53	4	0.3	4	0.3	1.13	0.86
Infection/ Pneumonia	9	22.2	6	11.9	1.86	0.24	16	1.4	9	0.7	2.05	0.086
Any SAE or Death	26	105.9	29	90.3	1.11	0.71	33	5.2	37	4.9	0.98	0.93
Patients at risk	46		57				46		56			

HEART FAILURE-RELATED HOSPITALIZATIONS – FOCUSED COHORT

Figure 5 illustrates the Kaplan-Meier curve for time to death or first HF related hospitalization. The curves separated early and demonstrate that the CorCap produced a statistically significant benefit on time to death or HF related hospitalization compared to control (p=0.042).

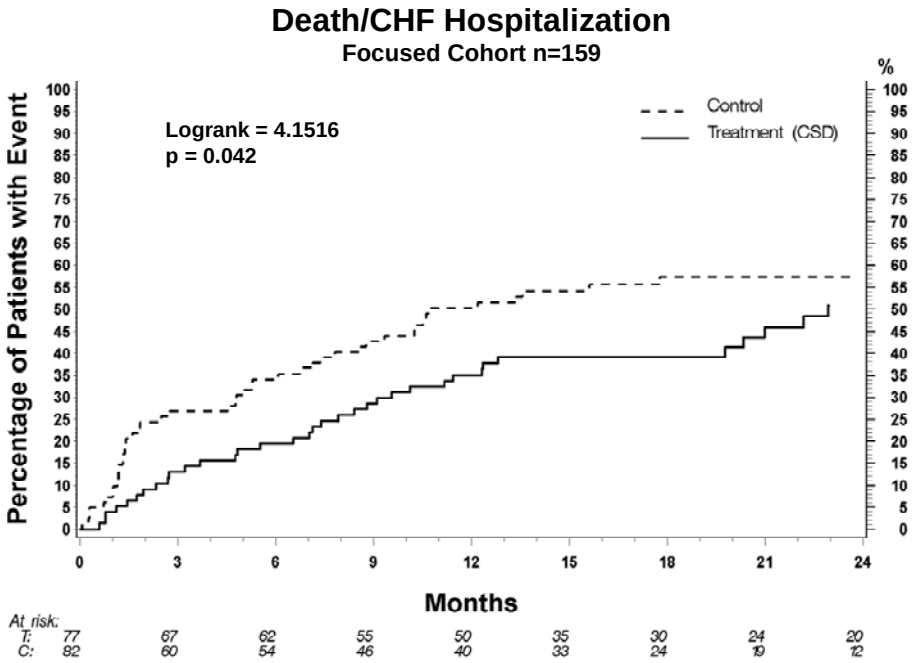


Figure 5: Death or Heart Failure Hospitalizations

Table 15 provides additional detail on heart failure related re-hospitalizations. During the median follow up period, the treatment group had fewer HF related hospitalizations (74 vs 82) and fewer total hospitalization days (445 vs 1441) and ICU days (75 vs 283). Because of the skew produced by several control patients with prolonged hospitalization, these differences were not statistically significant. However, the treatment group had a shorter median length of stay (3.0 vs 4.0 days) and a shorter mean length of stay (6.0 vs 17.6 days). These differences trended toward statistical significance (p=0.08).

Table 15: Heart Failure Related Re-Hospitalizations
Focused Cohort n=159

	Treatment (n=77)	Control (n=82)	p-value
Median Follow-up (months)	24.6	23.6	
Total # HF related Re-hospitalizations	74	82	0.70
Total # HF related Re-Hospitalization Days	445	1441	0.55
Total # HF related ICU Days	75	283	0.71
Median Length of Stay	3.0	4.0	p=0.08*
Mean Length of Stay	6.0	17.6	

*from a repeated-measures analysis of log-transformed data

PATIENT FUNCTIONAL ENDPOINTS – FOCUSED COHORT

Minnesota Living with Heart Failure (MLHF), SF-36 General Health Domain, & SF-36 Physical Function Domain

Figure 6, Figure 7, and **Figure 8** summarize the average treatment vs. control differences identified by longitudinal regression analyses for patient functional endpoints in the focused cohort by strata.

In the No MVR stratum for all three endpoints, the control group did not demonstrate any notable change, consistent with the fact that the control group did not receive any additional therapy. In contrast, the treatment group demonstrated an improvement in HF-specific quality of life, consistent with a benefit of the CorCap CSD.

In the MVR stratum, both the control and treatment group demonstrate improvements in quality of life; however, the treatment group demonstrated greater improvement, signaling that the CorCap CSD improved quality of life when added to MV surgery.

In the all patients analyses, the average treatment vs control differences for MLHF (p=0.0045) and SF-36 General Health Domain (p=0.0001) indicated that the CorCap CSD had a statistically significant effect on improving quality of life. Although the result for SF-36 Physical Function Domain was not statistically significant (P= 0.11), it was consistent with the other quality of life measures indicating that the CorCap CSD improves quality of life.

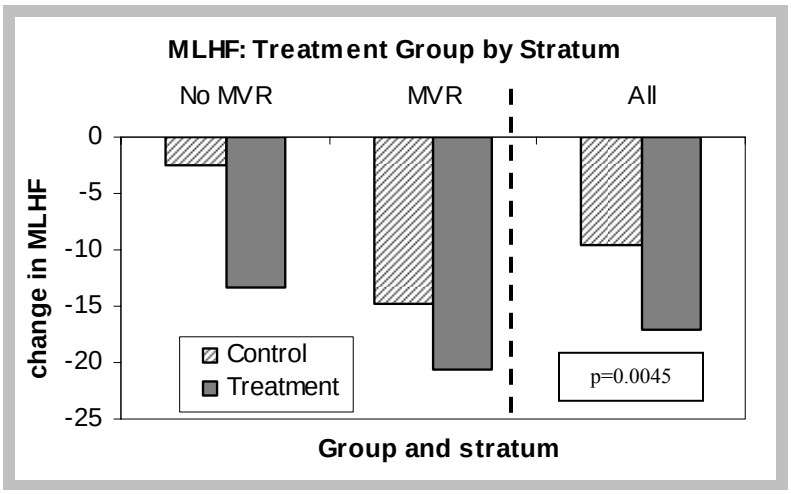


Figure 6: Treatment Difference with 95% CI for Minnesota Living with Heart Failure (units)

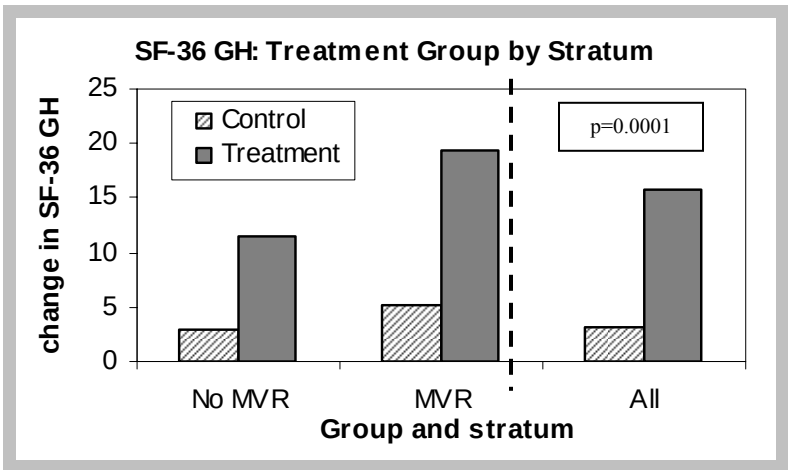


Figure 7: Overall Treatment Difference with 95% CI for SF-36 General Health Domain (units)

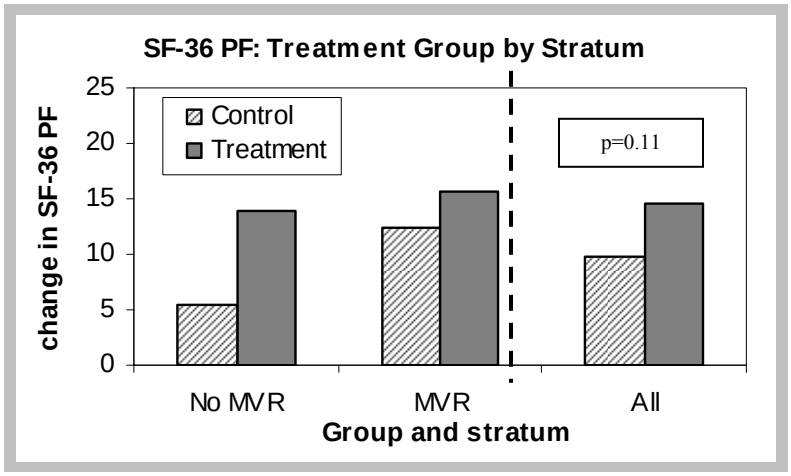


Figure 8: Overall Treatment Difference with 95% CI for SF-36 Physical Function Domain (units)

CARDIAC STRUCTURAL ENDPOINTS – FOCUSED COHORT

LVEDV

Figure 9, Figure 10, Figure 11, Figure 12, and **Figure 13** summarize the average treatment vs. control differences identified by longitudinal regression analyses for cardiac structural endpoints in the focused cohort by strata for LVEDV, LVESV, LVEF, Sphericity, and in LV Mass. In the No MVR stratum, the control group does not demonstrate any notable change consistent with the fact tht the control group did not receive any additional therapy. In contrast, the treatment group demonstrates a greater effect. This indicates that the CorCap CSD implant by itself can have a beneficial effect. In the MVR stratum, both the control and treatment groups demonstrate improvement; however, the treatment group demonstrates a greater effect, suggesting that the CorCap CSD had additive benefits to MV surgery.

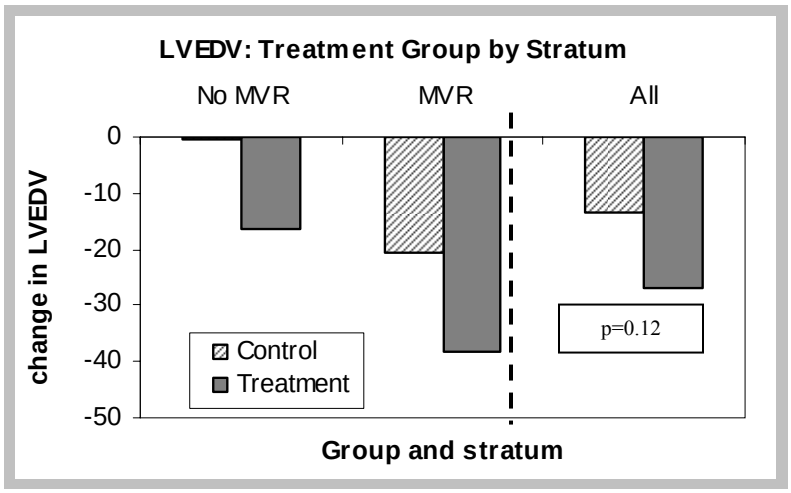


Figure 9: Overall Treatment Difference with 95% CI for LVEDV (ml)

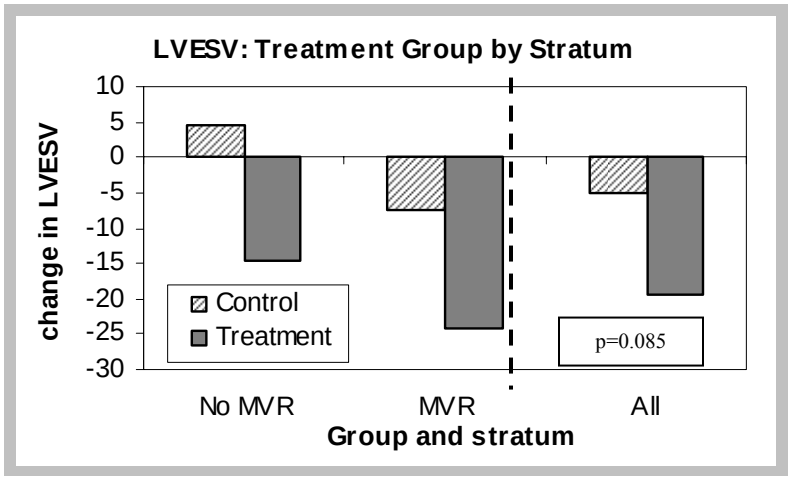


Figure 10: Overall Treatment Difference with 95% CI for LVESV (ml)

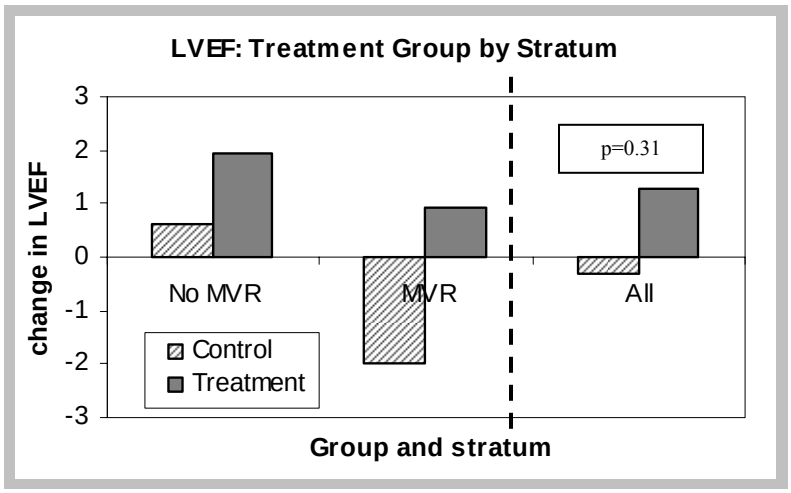


Figure 11: Overall Treatment Difference with 95% CI for LVEF (%)

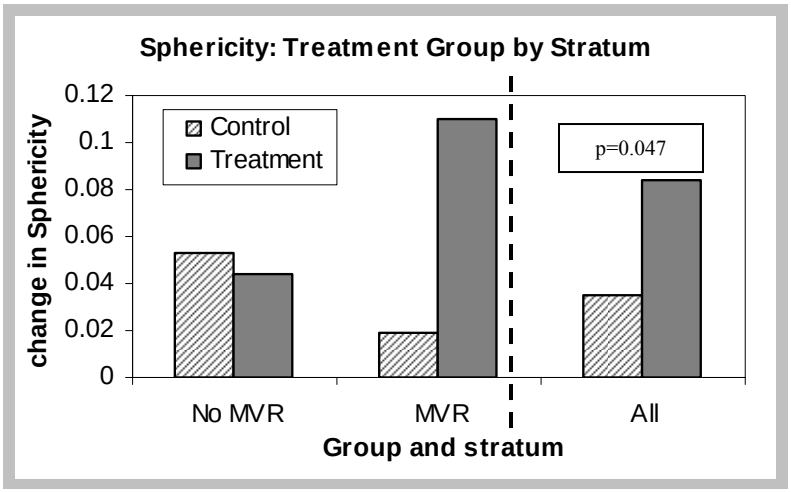


Figure 12: Overall Treatment Difference with 95% CI for Sphericity Index

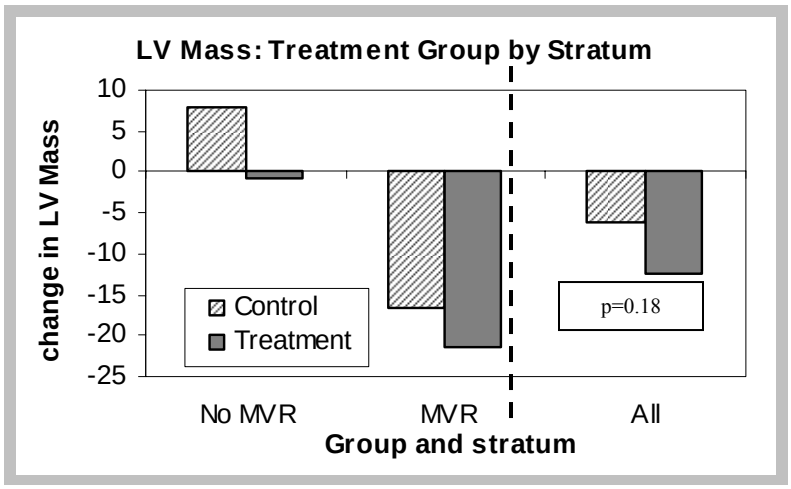


Figure 13: Overall Treatment Difference with 95% CI for LV Mass g/m^2 (indexed)

IMPLANT PROCEDURE

1. **Expose the Heart**

   The CorCap CSD can be implanted using standard sternotomy. After sternotomy, open the pericardium to expose the heart.

2. **Obtain Baseline LVEDD Using TEE**

   a. Using TEE, obtain baseline intra-operative left ventricular end-diastolic dimension (LVEDD) measurements using TEE at the mid-papillary muscle level.
   b. Using the CorCap sizer, measure the circumference of the heart at its largest diameter during end diastole. This measurement is typically near the AV groove.
   c. Measure the length of the heart from apex to base during end diastole.

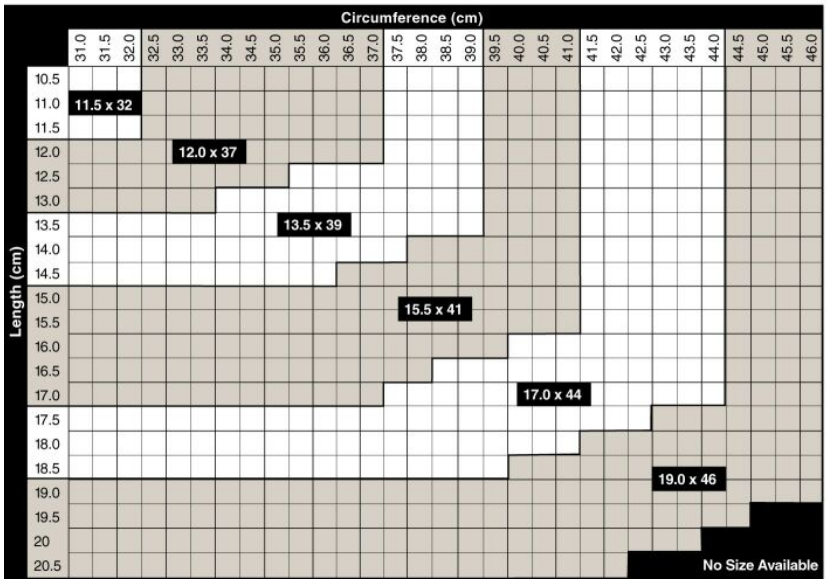
Note:

- Intraoperative conditions, including use of blood products, fluids and medications, may influence the size of the heart and therefore should be taken into account when obtaining baseline measurements.
- Ensure that sizing tool is placed at true apex to obtain accurate measurements.

3. **Select the Correct CorCap CSD Size**

   Compare the circumference and length measurements obtained in Steps 2b and 2c to the CorCap Size Selection Guide (Table 1) and select the device size indicated. If a patient measurement is between two sizes, choose the larger size.

Table 1. CorCap CSD Sizing Chart



CAUTION: Selection of a device that is smaller than indicated in the sizing chart may lead to inappropriate reduction in cardiac size, or necessitate intra-operative removal and replacement with an appropriately sized device.

4. **Concomitant Cardiopulmonary Bypass or Cardiac Surgery**
If cardiopulmonary bypass will be used or concomitant MVR surgery performed, review the "Special Conditions" section for related modifications to the implant procedure.

5. **Open CorCap CSD Package**
Check integrity of CorCap CSD package. Do not use if damage to package or seals is noted. Open the outer package and deliver the sterile inner package to the sterile field. Open the inner package.

6. **Inspect and Prepare the CorCap CSD**
   a. Inspect CorCap CSD for any irregularities. Do not use if device is torn, frayed or missing threads.
   b. Place CorCap CSD in sterile saline until ready for implant.

7. **Secure Hem of CorCap CSD to Heart**
   a. Position the CorCap CSD around the ventricles with the smooth side of hem and seam against the heart.
   b. Align device such that hem is positioned near level of the AV groove and seam is positioned on the anterior surface of the heart. Device length may extend beyond apex; this will be adjusted when new anterior seam is created (Steps 9-10). Do not shorten device by trimming hem.
   c. Starting at the most posterior location, secure the hem to the circumference of the heart near the AV groove using interrupted attachments every 2-4 cm.
   d. Work from side to side placing attachments around the circumference, moving towards the mid-anterior of the heart. The fabric should not wrinkle, pucker, or "scallop" between attachment points.
   e. To facilitate seam fitting later in the procedure, fabric located within 5cm of the seam should *not* be attached to the heart at this time.

WARNING: When securing device, ensure that attachments do not cause injury to coronary arteries.

WARNING: Manipulation of the heart may precipitate arrhythmias and/or hemodynamic compromise, particularly during placement of posterior attachments.

CAUTION: Use of an IABP is recommended in patients where manipulation of the heart could cause hemodynamic instability. If hemodynamic instability cannot be managed by pharmacological means or IABP, CPB is recommended.

Note: Taper point needles and 4.0 or stronger non-bioabsorbable suture material are recommended for suturing; taper cut or other cutting needles may cut CorCap CSD fabric fibers.

8. **Approximate Anterior Seam of CorCap CSD**
   a. Using CorCap™ fitting clamp, gather excess CorCap CSD fabric toward the anterior seam. (See **Figure 1**.)
   b. If device length extends beyond the apex, collect excess fabric into clamp.
   c. Check that the tension on the device is evenly distributed over the entire circumference of the CorCap CSD.
   d. The CorCap CSD should maintain complete contact with the ventricular walls throughout the cardiac cycle, with no gaps or redundant fabric.
   e. Measure LVEDD with TEE to anticipate final fit. Adjust the amount of gathered fabric within the clamp to ensure the appropriate degree of LVEDD reduction. Any change up to a 10% reduction is acceptable.

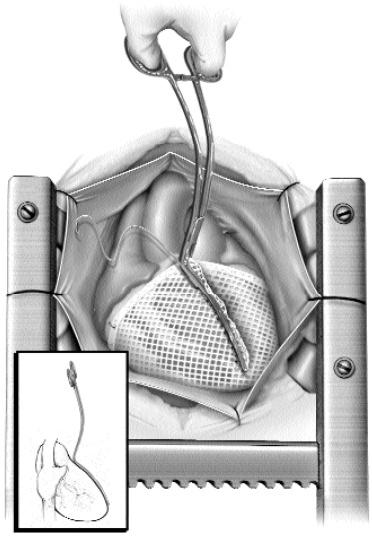


Figure 1: Approximate Anterior Seam

WARNING: Reduction in LVEDD should not exceed 10% as compared to baseline. Intraoperative conditions, including use of blood products, fluids and medications, may influence the size of the heart and therefore should be taken into account when approximating the CorCap CSD.

CAUTION: Do not decrease the apex to base dimension of the heart while approximating the anterior seam.

Note:
- The clamp should not be allowed to rest on the heart, as this could lead to errors in dimensional measurements.
- Use the CorCap fitting clamp for this procedure. Surgical clamps not specifically designed for this purpose could tear or snag the CorCap CSD fabric.

9. **Create New Anterior Seam**
With the CorCap fitting clamp in place, place a running mattress suture under the jaws of the CorCap fitting clamp, starting at the apex and continuing to the hem, to create a new anterior seam.

Note:
- Taper point needles and 4.0 or stronger non-bioabsorbable suture material are recommended for suturing; taper cut or other cutting needles may sever CorCap CSD fabric fibers.

10. **Trim Fabric**
    Keeping the CorCap fitting clamp in place, trim fabric above the clamp jaws. (See **Figure 2**.)

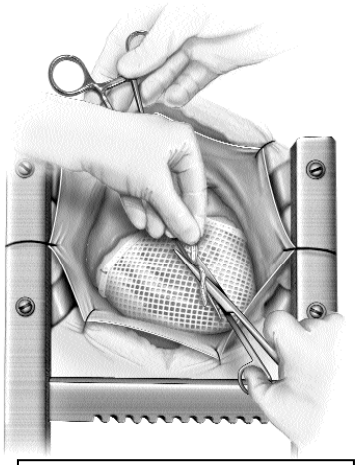


Figure 2: Trim Fabric

11. **Complete Final Anterior Attachment**
    Secure the device hem at the mid-anterior of the heart.
    near the AV groove using interrupted attachments every 2-4 cm.

> **WARNING**: When securing device, ensure that attachments do not cause injury to coronary arteries.

12. **Reinforce New Anterior Seam**
    a. Remove the CorCap fitting clamp. There should be approximately 3-5mm of fabric remaining above the running suture.
    b. Reinforce the new anterior seam by placing a running interrupted suture from the apex to the hem. (See **Figure 3**.) Stitch should provide redundancy and leave no gaps in seam, while maintaining even tension on the device.
    c. Continuously evaluate final fit (see step #13) during placement of this new anterior seam. Adjust suture placement accordingly.

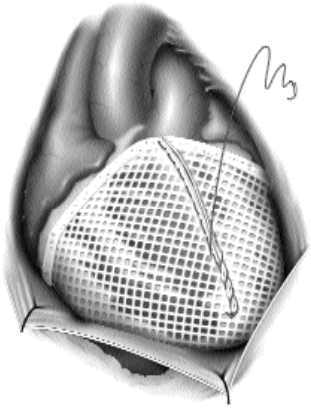


Figure 3: Reinforce New Anterior Seam

13. **Evaluate Final Fit of the CorCap CSD**
    a. Evaluate fit using the Fabric Tension Test ("tent test").
        - Using a blunt surgical instrument, gently lift fabric approximately 1-2 cm off the heart.
        - Release the "tent" – it should re-conform to the surface of the heart within 1-2 cardiac cycles.
        - Repeat this test in several locations away from the hem and seams of the CorCap CSD.
    b. The CorCap CSD should cover both ventricles with no gaps between the device and the heart throughout the entire cardiac cycle.

14. **Measure Final Fit of the CorCap CSD**
    a. Measure LVEDD with TEE at the same location used to obtain the baseline circumference measurement in Step 2. While use of TEE is strongly recommended, heart size may be determined by measuring the circumference of the heart at its largest diameter (during end-diastole).

> **WARNING:** Reduction should not exceed 10% as compared to baseline LVEDD. Intraoperative conditions, including use of blood products, fluids and medications, may influence the size of the heart and therefore should be taken into account when fitting the CorCap CSD.

    b. If reduction in LVEDD of greater than 10% is noted, remove sutures from the anterior seam and adjust fit. If suture removal damages the CorCap CSD or if there is not enough fabric to recreate a 3-5 mm seam, remove device and repeat procedure with a new device.

15. **Perform Final Inspection**
    a. Remove any excess particulate matter that is found in-situ.

b. Ensure that any fabric or seam damage is repaired
c. Visually inspect the device and device hem to ensure that the device fits uniformly over all surfaces of the ventricles.

SPECIAL CONSIDERATIONS

1. **Cardiopulmonary Bypass**
   If cardiopulmonary bypass is used, the following considerations are advised:
   a. Baseline heart size measurements (Step 2) and size selection (Step 3) should be made before placing the patient on bypass. If this is not possible, heart should be filled to an approximation of baseline.
   b. Fitting of the device (Steps 8-12) should not be performed until patient is off bypass and has a full, stable beating heart.

2. **Mitral Valve Repair/Replacement (MVR)**
   If concomitant mitral valve repair or replacement is indicated, the following considerations are advised:
   c. Baseline heart size measurements (Step 2) and size selection (Step 3) should be made before placing the patient on bypass. If this is not possible, heart should be filled to an approximation of baseline.
   a. To minimize need for cardiac manipulation following placement of mitral valve prosthesis, position CorCap CSD and place posterior attachments prior to valve replacement or repair.
   b. Fitting of the device (Steps 8-12) should not be performed until patient is off bypass and has a full, stable beating heart post-MVR.

DEVICE NOTES

- The CorCap CSD is provided sterile and is for single use only.
- The CorCap CSD may not be resterilized.
- The CorCap CSD is latex free.
- The CorCap CSD is MRI compatible.
- The CorCap CSD is nuclear scan-compatible.
- The CorCap CSD does not complicate future cardiac catheterization.

WARRANTY

Acorn Cardiovascular, Inc.™, has taken reasonable care in the design and manufacture of this product. Other than this representation, there are NO EXPRESS OR IMPLIED WARRANTIES INCLUDING, WITHOUT LIMITATION, and WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.

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MANUFACTURER

Acorn Cardiovascular, Inc.
601 Campus Drive
St. Paul, Minnesota 55112 USA
Tel: 651.286.4800
Fax: 651.286.4848
www.acorncv.com

AUTHORIZED EU REPRESENTATIVE

MedPass International Limited
Windsor House, Barnett Way, Barnwood
Gloucester GL4 3RT
United Kingdom

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