

CardioMEMS Champion™ HF Monitoring System

FDA Review of P100045

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FDA Presentations

The FDA presentation will be in two parts.

- Presentation of FDA analysis of sponsor study results.
- Presentation of important aspects of study conduct that many have an impact on the interpretation of study results.

Trial Conduct and FDA Analysis

- NOTE: The FDA Analysis of the sponsor's clinical trial data was performed without consideration of the trial conduct issues that will be presented at the end of the FDA's presentation.
- NOTE: FDA does not consider economic impact in deliberating whether to approve a device.

FDA Presentations

- Introduction - CDR James Cheng
- Statistical Overview - Dr. Yonghong Gao
- Clinical Results and Considerations - Dr. Randall Brockman
- Medical Treatment - Dr. Ileana Piña
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Proposed Indications for Use

- The CardioMEMS Champion™ HF Monitoring System is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and to reduce heart failure hospitalizations.
- The CardioMEMS Champion™ HF Monitoring System is used by the physician in the hospital or office setting to obtain and review PA pressure measurements. The CardioMEMS Champion™ HF Monitoring System is used by the patient in the home or other remote location to wirelessly obtain and send hemodynamic and PA pressure measurements to a secure database for review and evaluation by the patient's physician.

Pre-Clinical Review

- Pre-clinical testing included
 - Software Validation
 - Biocompatibility testing
 - Electrical, mechanical, and environmental *in-vitro* bench testing
 - Sterilization testing
 - Packaging and Shelf-life testing
 - Animal testing
- No outstanding pre-clinical issues

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CardioMEMS Champion™ HF Monitoring System Statistical Analysis

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CDRH/FDA
December 8, 2011

Study Overview 1

- Two-arm randomized trial
- 270 subjects in treatment arm and 280 subjects in control
- Single-blind: patients are blinded to the randomization
- Objective: superiority (effectiveness) to standard of the care
- Outcome: number of hospitalizations per subject 6-month

Primary Endpoints

- Primary safety endpoint 1: performance goal
 - $H_0: \pi$ (Freedom from DSRC at six months) $\leq 80\%$
 - $H_1: \pi$ (Freedom from DSRC at six months) $> 80\%$
- Primary safety endpoint 2: performance goal
 - $H_0: \pi$ (Freedom from sensor failure at six months) $\leq 90\%$
 - $H_1: \pi$ (Freedom from sensor failure at six months) > 90
- Primary effectiveness endpoint: Superiority hypotheses:
 - $H_0: \mu$ (TREATMENT) = μ (CONTROL)
 - $H_a: \mu$ (TREATMENT) $\neq \mu$ (CONTROL)
- Study success criteria: meet all three primary endpoints

Study Overview 2

- Planned Interim Analysis
 - When half of pts have 6-month follow-up, look at primary safety and effectiveness endpoints
 - O'Brien-Fleming boundaries were used: p-values for the interim and final analyses were set at 0.005 and 0.048
- Secondary Endpoints
 - Change from baseline in pulmonary artery pressures
 - Proportion of subjects hospitalized for heart failure
 - Days alive outside of the hospital
 - Quality of Life: Minnesota Living with Heart Failure Questionnaire (MLHFQ)
- Only if all primary endpoints are met, a hierarchical testing procedure for secondary endpoints was planned and was to stop once a type I error rate exceeding 0.05 was found

Trial Conduct and FDA Analysis

- NOTE: The FDA Analysis of the sponsor's clinical trial data was performed without consideration for the trial conduct issues that will be presented at the end of the FDA's presentation.

Primary Safety Endpoint 1

- Primary safety endpoint 1: rate of device/system related complications (DSRC) at 6-month
 - $H_1: \pi$ (Freedom from DSRC at six months) > 80%
- Exact test, at significance level of 0.048
- Result:
 - 567 (98.6%) of 575 patients event-free
 - exact 95.2% CI: (97.3%, 99.4%)
- This endpoint was met

Primary Safety Endpoint 2

- Primary safety endpoint 2: freedom of sensor failure at 6-month
 $H_1: \pi$ (Freedom from sensor failure at six months) $> 90\%$
- Exact test, at significance level of 0.048
- Result:
 - Out of 550 sensors implanted, all were operational
 - exact 95.2% CI: (99.3%, 100%)
- This endpoint was met

Primary Effectiveness Endpoint

- Rate of heart failure related hospitalizations at 6-month

$$H_a: \mu (\text{TREATMENT}) \neq \mu (\text{CONTROL})$$

- Data:

	Treatment (270)	Control (280)
# of event	84	120
Events/patient-6-month	0.32	0.44

Data Modeling

- Primary effectiveness endpoint: # of HFR hospitalization within 6-month follow-up
- Patients had variable follow-up time
- Pre-specified analysis model:
 - Negative Binomial Regression
 - Dependent variable: # of hospitalization
 - Predictors: treatment, 6-month follow-up time
- Sponsor's negative binomial regression:
 - p-value for treatment effect: 0.0002

Models FDA Evaluated

- Basic Poisson regression
- Poisson regression, variance scaled to correct over-dispersion
- Zero-inflated Poisson regression
- Basic Negative Binomial regression
- NB regression, variance scaled to correct over-dispersion
- Zero-inflated NB regression
- Nonparametric (bootstrap)

Model Summary

Model	P-value for treatment
Sponsor's negative binomial model	0.0002
Basic Poisson	0.0227
Variance-Scaled Poisson	0.0348
Zero-Inflated Poisson Zero-Inflated NB	0.0107 for zero-model
Basic Negative Binomial	0.1137
Variance-Scaled Negative Binomial	0.0557
Nonparametric (bootstrap)	0.070

Robustness of Effectiveness

- The sponsor's analysis of the primary effectiveness endpoint is not robust with respect to the methods used to estimate the parameters of the negative binomial model.
- In the sponsor's analysis, if 13 more HFR hospitalizations (from 80 to 93) are added at random to the patients in the Treatment arm, the result is no longer statistically significant at 0.048.
- For the bootstrap model if only two hospitalizations are added to the Treatment arm the p-value exceeds 0.1.

Secondary Endpoints

- Since all primary endpoints appear to have been met, the following secondary endpoints were tested hierarchically at the significance level of 0.05, and the testing order is the following
 - Change from baseline in pulmonary artery pressures
 - Proportion of subjects hospitalized for heart failure
 - Days alive outside of the hospital
 - Quality of Life- Minnesota Living with Heart Failure Questionnaire (MLHFQ)
- It appears that four secondary endpoints were met

Robustness of Secondary Effectiveness

For secondary endpoint #2 (proportion of subjects hospitalized with heart failure)

- If the number of hosp. patients in the Treatment arm is increased by only 3 (from 55 to 58 out of 270 versus 80 out of 280), the p-value is no longer significant at 0.05.

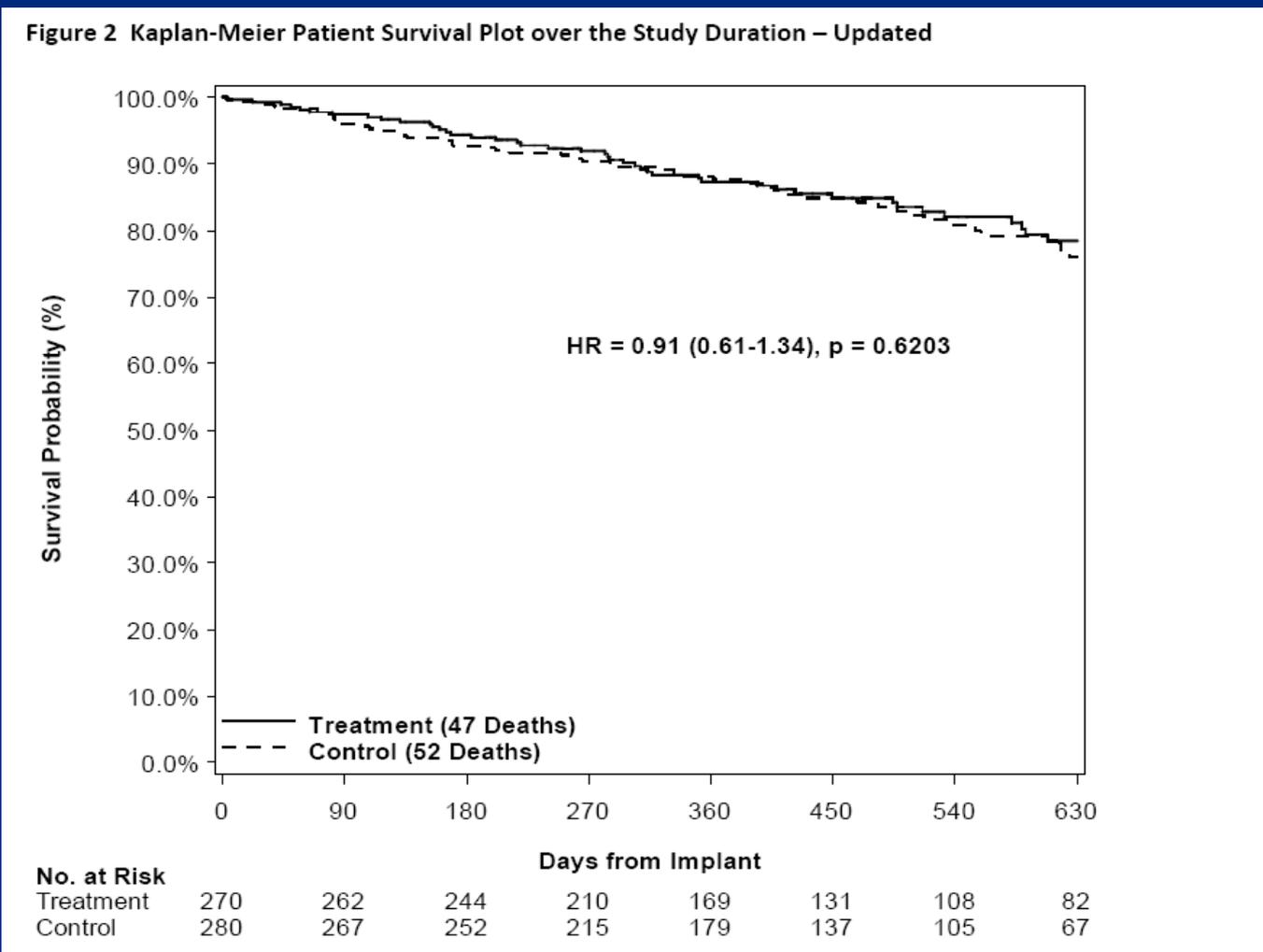
Supplementary Analyses

Sponsor conducted the following supplemental analyses:

- Survival analysis
- HFR hospitalization-free survival analysis
- Sensor performance analysis
- Gender analysis for HFR hospitalization

Survival Analysis

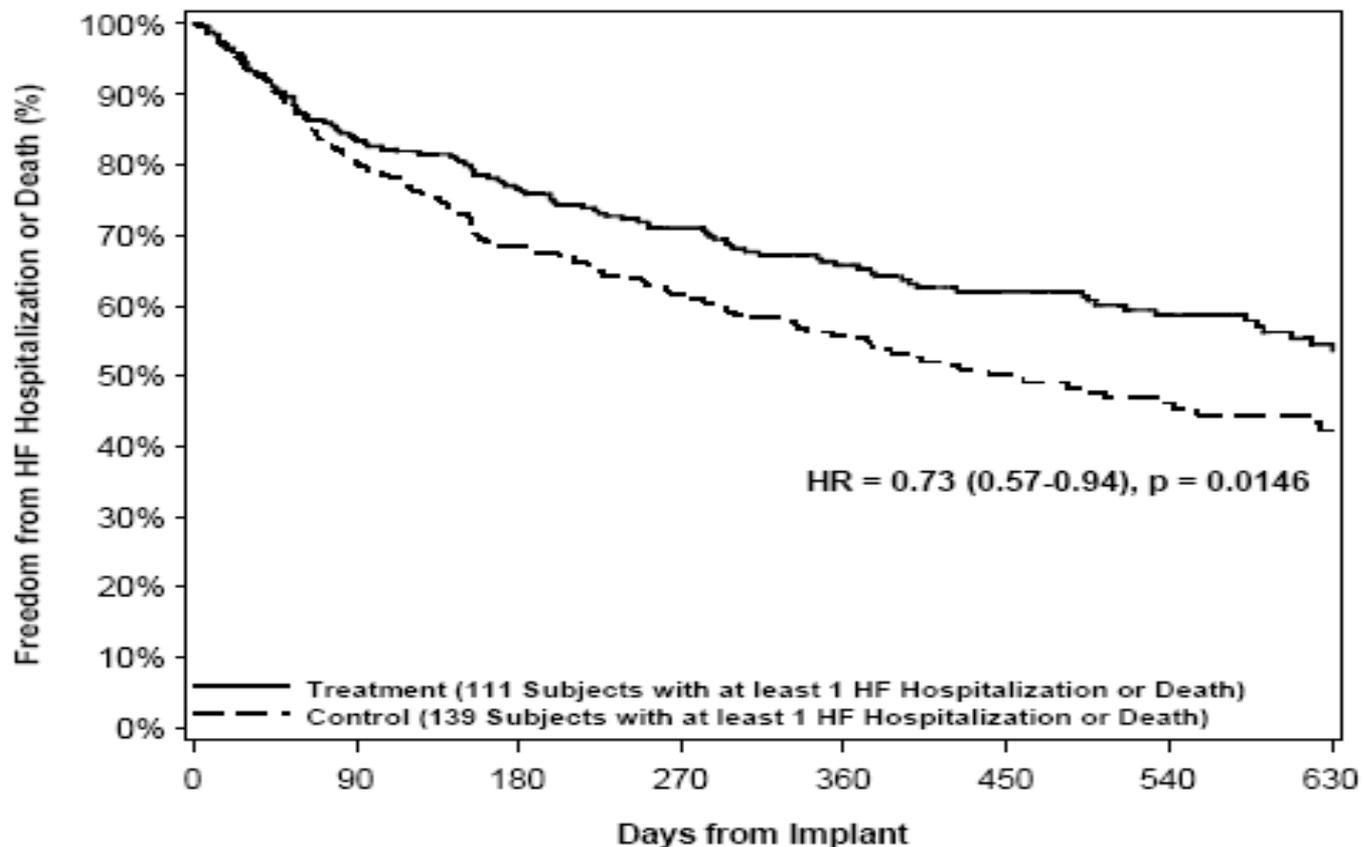
- There was no statistically significant difference in survival between the treatment and control groups over study duration.



HFR Hospitalization-Free Survival Analysis

- The treatment demonstrated a significant benefit in reducing time to death or first HFR hospitalization.

Figure 19. Freedom from HF Hospitalization or Death Over the Study Duration

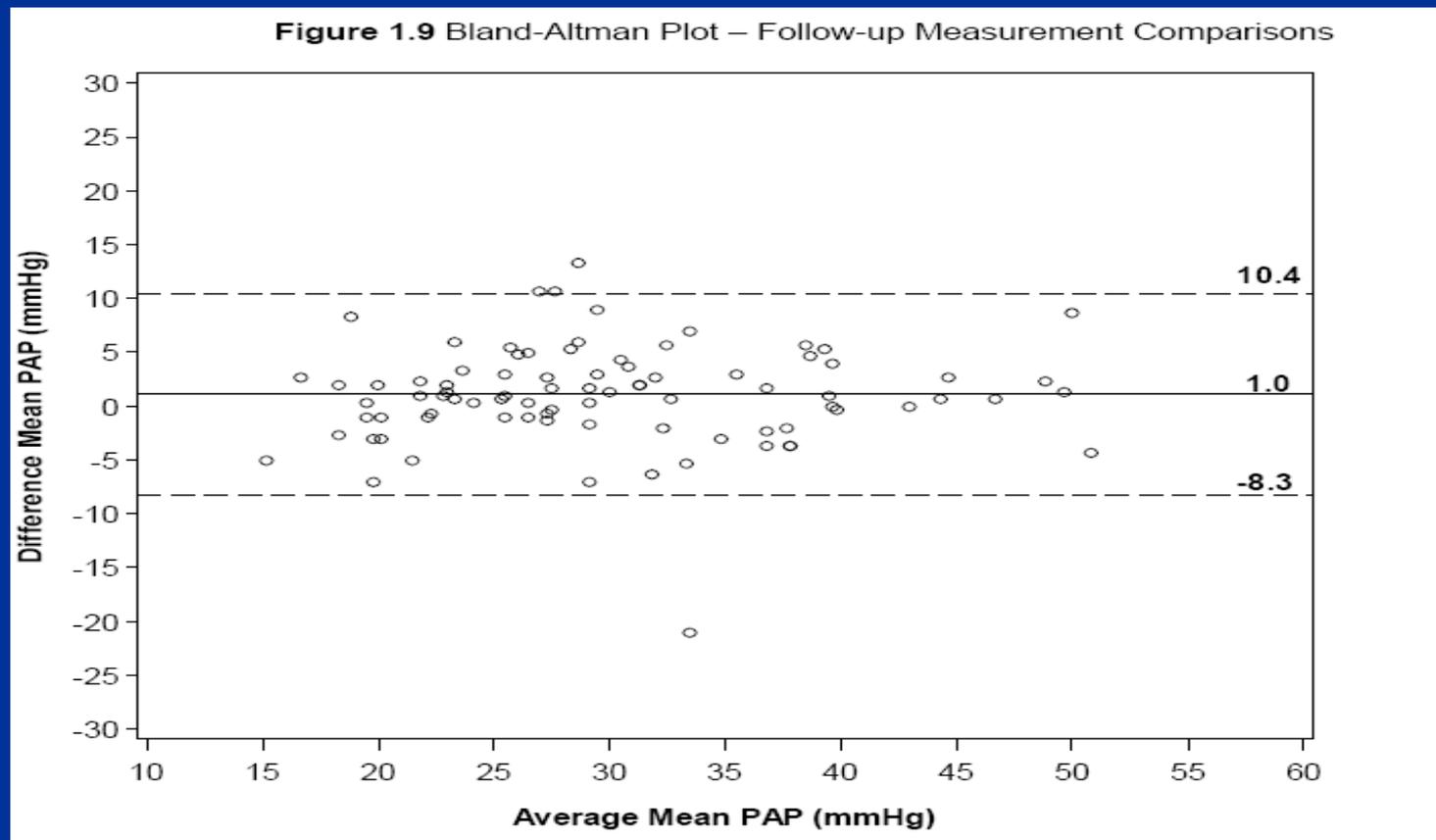


No. at Risk

Treatment	270	225	201	168	130	104	83	62
Control	280	223	186	145	112	79	56	38

Sensor Performance Analysis

- Comparative data of a subset of 43 patients who underwent 85 physician initiated Right heart catheterization using Swan-Ganz PA mean measurement were provided in the following Bland-Altman plot: mean of 1.0mmHg



Gender Analysis

- The HFR hospitalization rate (events/person-6-month) was assessed, stratified by gender

	Treatment (270)	Control (280)	p-value
Males (399)	60 events 194 patients Rate: 0.32	106 events 205 patients Rate: 0.53	P- value of Trt*gender interaction test: 0.0108
Females (151)	24 events 76 patients Rate: 0.32	14 events 75 patients Rate: 0.19	

- Control arm: event rates were quite different for males and females

Primary Effectiveness Analysis Stratified by Gender

FDA's analysis:

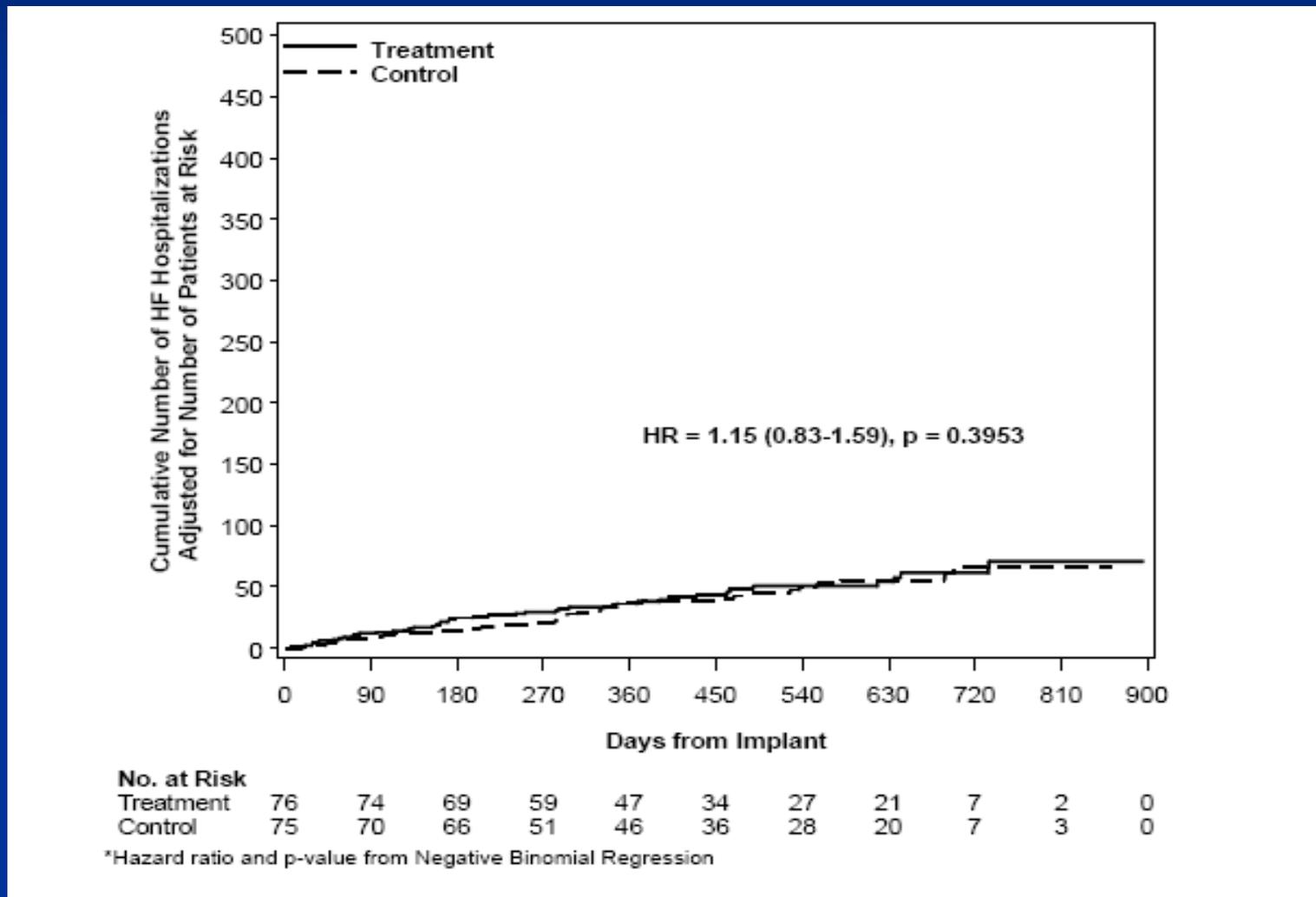
Gender	Point estimate: IRR	95% CI: IRR	2-sided P-value: treatment
Males	1.668	(1.215, 2.289)	0.0034
Females	0.603	(0.312, 1.167)	0.1466

Distribution of # of Hosp.

# of Hosp	0	1	2	3	4	5
Female, Trt 76	62 (.816=62/76)	8 (.105)	4 (.053)	1 (.013)	0 (0)	1 (.013)
Female, Cont. 75	64 (.853)	9 (.12)	1 (.013)	1 (.013)	0 (0)	0 (0)
Male, Trt. 194	153 (.789)	26 (.134)	12 (.062)	2 (.013)	1 (.005)	0 (0)
Male, Cont. 205	136 (.663)	42 (.205)	19 (.093)	6 (.029)	2 (.009)	0 (0)
Overall	415 (.755)	85 (.155)	36 (.065)	10 (.018)	3 (.005)	1 (.0018)

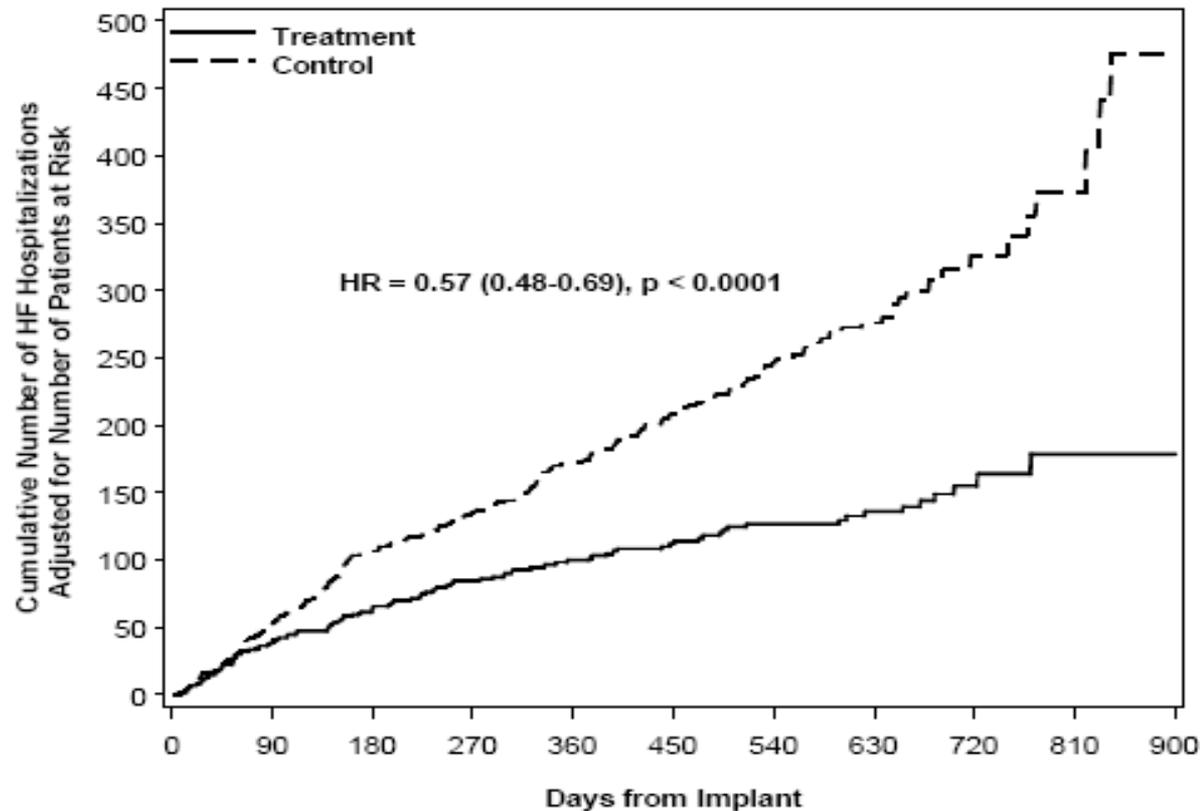
Cumulative HFR Hospitalization: Female

- There is no statistically significant difference between two arms in cumulative HFR hospitalization for females



Cumulative HFR Hospitalization: Male

- There is a statistically significant difference between two arms in cumulative HFR hospitalization for males



No. at Risk	0	90	180	270	360	450	540	630	720	810	900
Treatment	194	188	175	151	122	97	81	61	22	3	1
Control	205	197	186	164	133	101	77	47	18	7	0

*Hazard ratio and p-value from Negative Binomial Regression

Gender Analysis Summary

- For HFR hospitalization rate at 6-month, data indicated different treatment effect in males and females; intervention reduced hospitalization rate for males, but there was a non-statistically significant increase for females.
- For cumulative hospitalization over study duration, data indicated different treatment effect in males and females; intervention reduced # of hospitalizations for males, but not for females.

Summary of Statistical Inference

- General concerns on study conduct, should be taken into account when interpreting results
- The trial appeared to meet the primary endpoints
- The trial appeared to meet the secondary endpoints
- Significant intervention by gender interaction
 - Significant, positive effect for males, non-significant negative effect for females

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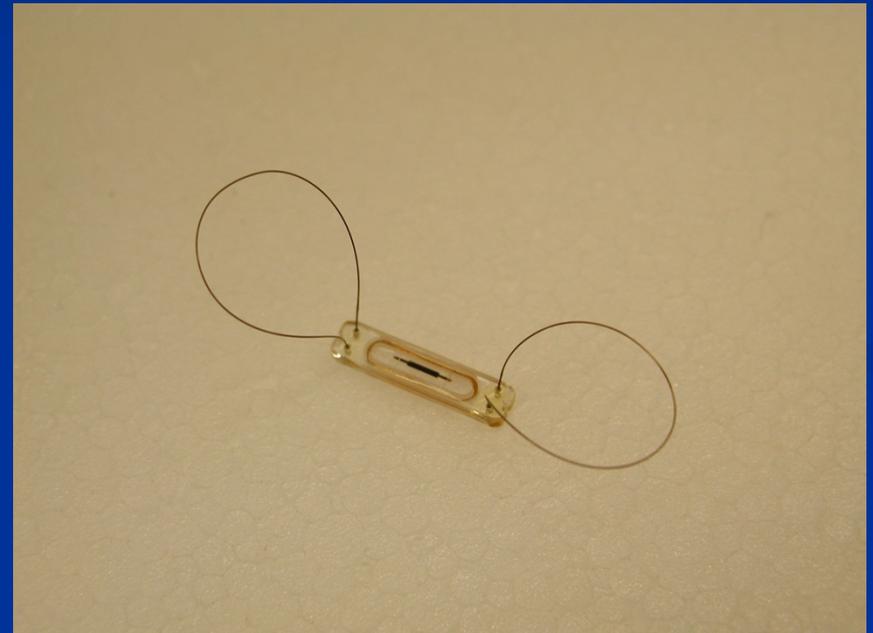
FDA Clinical Review of the CardioMEMS Champion™ HF Monitoring System

PMA P100045

Randall G. Brockman, M.D.
Medical Officer, CDRH/ODE/DCD

Champion™ HF Monitoring System

- Wireless Implantable Hemodynamic Sensor/Monitor (Sensor)
- External Patient/Hospital Measurement System
- Patient Data Management System



Dimensions of the sensor are 15mm in length, 3.4mm in width and 2mm in thickness

IDE Clinical Study

- CHAMPION: CardioMEMS Heat Sensor Allows for Monitoring of Pressure to Improve Outcomes in NYHA class III heart failure patients
 - Randomized, controlled trial
 - 550 subjects
 - All subjects received the PA sensor
 - Treatment subjects managed using PA pressure data
 - Control subjects managed using standard HF therapy

IDE Clinical Study

- Enrollment criteria
- Demographics
- Endpoints
 - Primary Safety
 - Additional Safety Analyses
 - Primary Effectiveness
 - Secondary Effectiveness
- Medication (Dr. Pina)
- Potential Bias

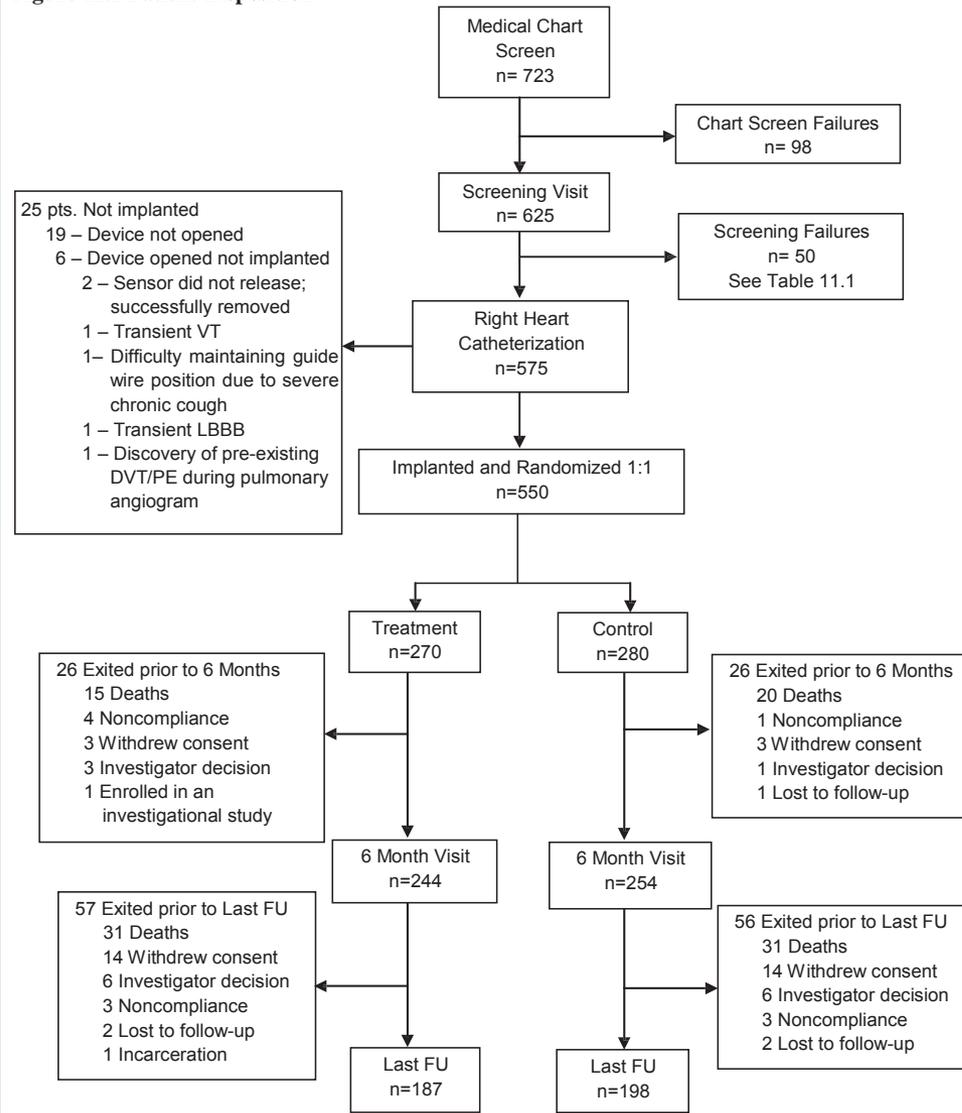
Inclusion / Exclusion Criteria

- Inclusion
 - NYHA class III
 - At least 1 Heart Failure Related (HFR) hospitalization within 1 year
 - Appropriate background HF medical therapy
- Exclusion
 - Glomerular Filtration Rate < 25 ml/min who are non-responsive to diuretics or who are on dialysis
 - History of recurrent (>1) PE or DVT

Note – Enrollment was not contingent on LVEF; patients with heart failure and preserved ejection fraction were included

Patient Accountability

Figure 11.1 Patient Disposition



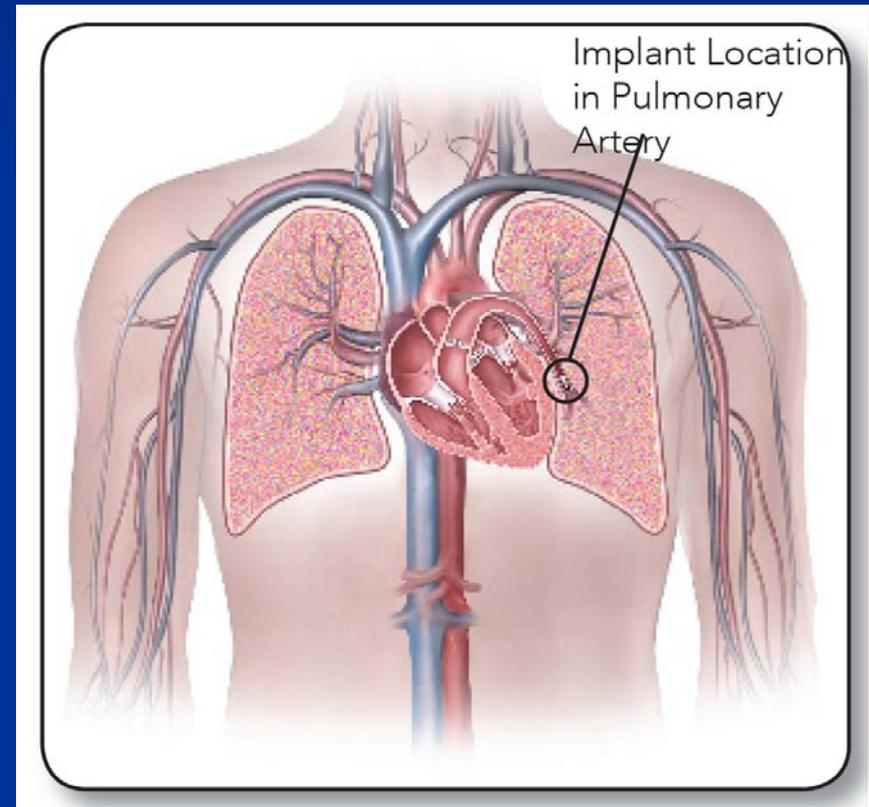
Baseline Demographics

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value[1]
Age (years)	61.3 ± 13.0 (270)	61.8 ± 12.7 (280)	61.6 ± 12.8 (550)	0.5927
Gender				
Male	194 (71.9%)	205 (73.2%)	399 (72.5%)	0.7745
Female	76 (28.1%)	75 (26.8%)	151 (27.5%)	
Race				
White	196 (72.6%)	205 (73.2%)	401 (72.9%)	0.9236
African Descent	68 (25.2%)	58 (20.7%)	126 (22.9%)	
CRT or CRT-D	91 (33.7%)	99 (35.4%)	190 (34.5%)	0.7201
ICD	88 (32.6%)	98 (35.0%)	186 (33.8%)	0.5889
Ejection Fraction				
Reduced (<40%)	24.4 ± 7.4 (208)	22.3 ± 7.0 (222)	23.3 ± 7.3 (430)	
Preserved (≥40%)	50.5 ± 9.2 (61)	50.8 ± 9.2 (57)	50.6 ± 9.1 (118)	

[1] P-value testing Treatment vs. Control obtained from exact Wilcoxon Rank-Sum Test for continuous measures and Fisher's exact test for categorical measures. 41

Sensor Implantation Procedure

- Right Heart Catheterization (RHC)
- Pulmonary Angiogram
- Delivery catheter advanced over guidewire
- Sensor is released



Safety Results

- Primary Safety #1: Freedom from a device/system-related (DSRC) complication through 6 months
- Primary Safety #2 : Freedom from pressure sensor failures through 6 months
 - Defined as “A pressure sensor failure occurs when the sensor malfunctions to the point that no readings can be obtained from it after all attempts are exhausted including troubleshooting the system to rule out any problems with the electronic components.”

Primary Safety Endpoint #1

- Freedom from a device/system-related (DSRC) complication through 6 months
- The analysis population included all patients that underwent a RHC, whether or not the sensor was implanted (N=575)
- Protocol included a performance goal of 80% of patients that could experience a primary safety event
- Protocol included a definition for this endpoint

Primary Safety #1

	Analysis Population (N=575)	P-value
Device/System Related Complication – 6 months	1.4% (8/575)	
Freedom from DSRC – 6 months	98.6% (567/575)	
95.2% LCB	97.3%	< 0.0001
Performance goal	80%	
<i>Primary Safety Endpoint #1 was met</i>		

Device/System Related Complications (DSRC)

DSRC	Description	Treatment	Outcome
Sensor did not fully deploy	Sensor remained slightly attached to delivery catheter	Removed with a snare	Recovered without sequelae
TIA	TIA; INR was subtherapeutic	Anticoagulation to therapeutic INR	Recovered
Atypical Chest Pain	Atypical chest pain	Imdur, analgesics	Recovered
Hemoptysis	Hemoptysis during implant secondary to severe chronic cough	Bronchoscopy; well formed thrombus positive for Klebsiella. Treated with irrigation, suction, antibiotics	Recovered without sequelae
Sepsis	Worsening respiratory distress, hemodynamic instability, sepsis	Antibiotics, diuretics, inotropes, nebulizers	Family requested DNR; care was withdrawn
Wide complex tachycardia	Worsening cardiopulmonary disease secondary to arrhythmia (thought to be atrial dysrhythmia)	Amiodarone, diuretics, dopamine, BiPAP	Family requested DNR ; care was withdrawn
Arterial embolism	Right upper extremity arterial thrombus; INR was subtherapeutic	Thrombectomy; anticoagulation to therapeutic INR	Recovered without sequelae
In-situ thrombus	CTA revealed a small filling defect secondary to injury from the Swan-Ganz balloon	Anticoagulation to therapeutic INR	Recovered without sequelae

Primary Safety Endpoint #2

- Freedom from pressure sensor failures through 6 months
- The analysis population included all patients that had the sensor implanted (N=550)
- Protocol included a performance goal of 90%
- Protocol included a definition for this endpoint

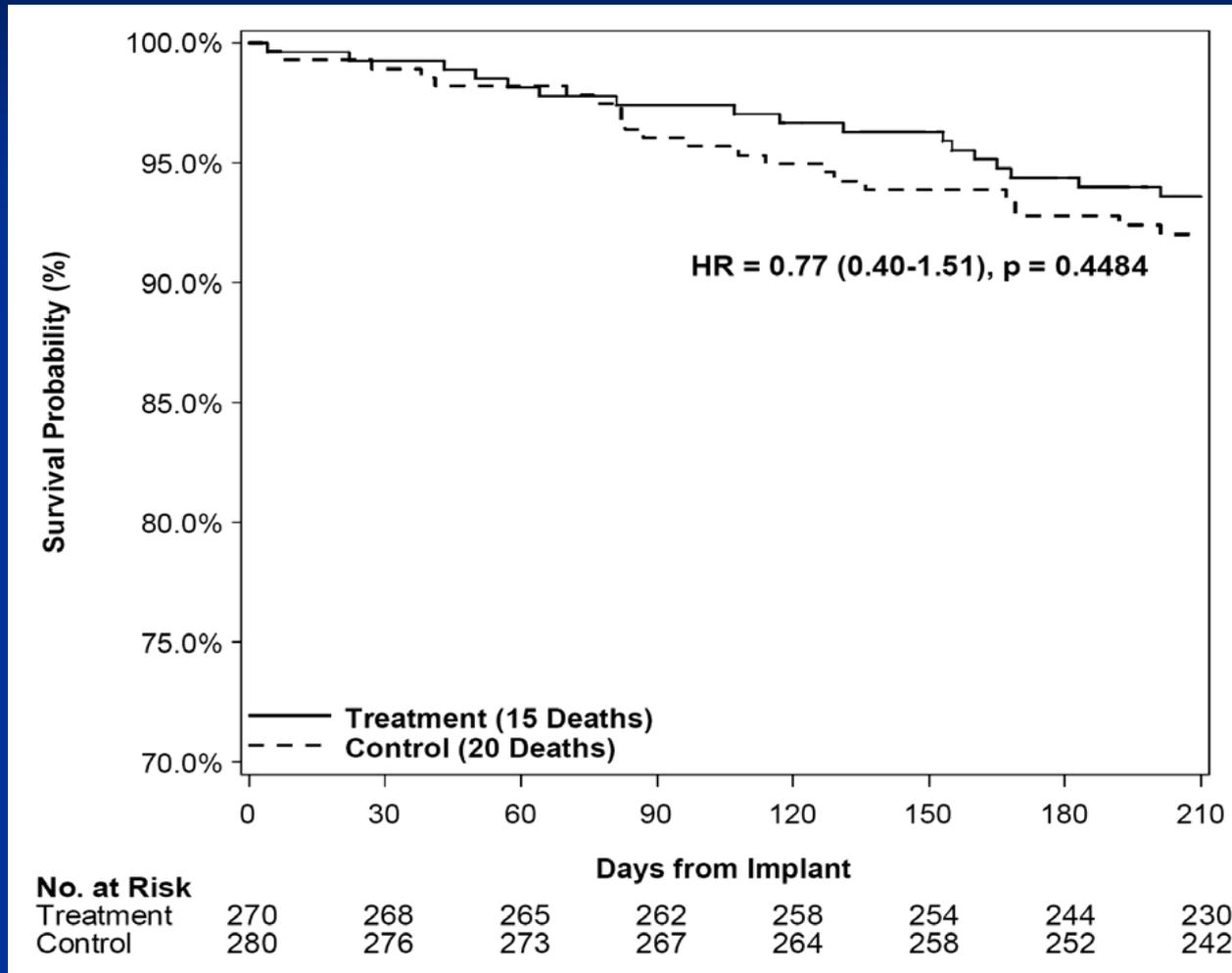
Primary Safety #2

	Analysis Population (N=550)	P-value
Pressure Sensor Failures – 6 months	0% (0/550)	
Freedom from Pressure Sensor Failure – 6 months	100% (550/550)	
95.2% LCB	99.3%	< 0.0001
Performance goal	90%	
<i>Primary Safety Endpoint #2 was met</i>		

Survival Through 6 Months

- 15 deaths among 270 Treatment patients
- 20 deaths among 280 Control patients
- Death rates were similar between the two arms.
- The overall proportion of deaths was 6.4% through 6 months.
- FDA believes the overall mortality rate in the current study compares reasonably well to published reports of similar patient populations with advanced heart failure, prior heart failure hospitalization and severe LV systolic dysfunction.

Survival Through 6 Months

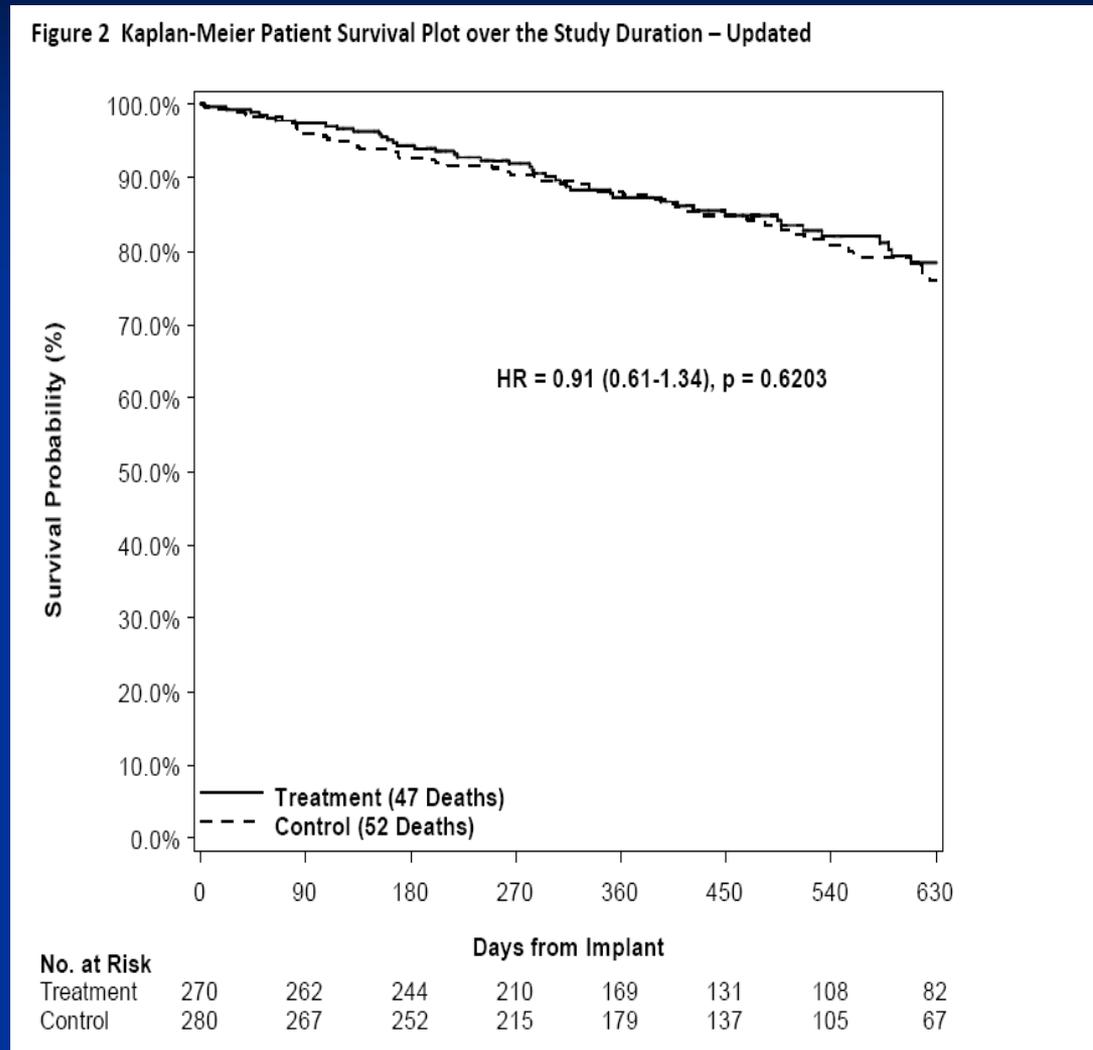


Survival was similar between the treatment and control groups through 6 months.

CEC Adjudication of Mortality at 6 Months

	Treatment (270)	Control (280)	Total (550)
Total Subject Deaths	15 (5.6%)	20 (7.1%)	35 (6.4%)
Cause of Death			
Heart Failure	9 (3.3%)	6 (2.1%)	15 (2.7%)
Sudden Death	3 (1.1%)	6 (2.1%)	9 (1.6%)
Cardiac Procedure	0 (0.0%)	1 (0.4%)	1 (0.2%)
Cardiac-Other	0 (0.0%)	1 (0.4%)	1 (0.2%)
Non-Cardiac	3 (1.1%)	6 (2.1%)	9 (1.6%)

Survival Analysis over Study Duration



There was no statistically significant difference in survival between the treatment and control groups over the whole study duration.

Serious Adverse Events Through 6 Months

	Treatment (270)	Control (280)	Total (550)
Subjects	121 (44.8%)	155 (55.4%)	276 (50.2%)
Events	339	385	724

The Most Common SAEs Prior to 6 Months

	Treatment (270)		Control (280)		Total (550)	
	Subjects	Events	Subjects	Events	Subjects	Events
CHF	59 (21.9%)	105	82 (29.3%)	130	141 (25.6%)	235
MI/ACS/Chest Pain	16 (5.9%)	21	19 (6.8%)	25	35 (6.4%)	46
Ventricular Arrhythmia	6 (2.2%)	6	11 (3.9%)	16	17 (3.1%)	22
Pulmonary Infections	9 (3.3%)	11	11 (3.9%)	12	20 (3.6%)	23
Renal Dysfunction/Failure	16 (5.9%)	16	10 (3.6%)	10	26 (4.7%)	26
Hypotension	8 (3.0)	11	7 (2.5%)	8	15 (2.7%)	19
Dehydration	5 (1.9%)	6	1 (0.4%)	1	6 (1.1%)	7

Procedure-Related Adverse Events

- Sponsor reported seven (7) procedure-related AEs
 - hemoptysis
 - AF
 - cardiogenic shock
 - fever
 - groin hematoma/pain (2)
 - prolonged hospitalization to restart warfarin

Renal Function

	Treatment (270)	Control (280)	Total (550)
Screening Creatinine (mg/dL)	1.40±0.47 (270)	1.35±0.42 (280)	1.38±0.44 (550)
6 Month Creatinine (mg/dL)	1.49±0.57 (230)	1.41±0.53 (235)	1.45±0.55 (465)
6 Month Creatinine Change from Screening (mg/dL)	0.10±0.45 (230)	0.07±0.38 (235)	0.08±0.42 (465)
Screening GFR (mL/min/1.73m ²)	60.4±22.5 (270)	61.8±23.2 (280)	61.1±22.9 (550)
6 Month GFR (mL/min/1.73m ²)	57.3±22.5 (230)	61.7±26.1 (235)	59.5±24.5 (465)
6 Month GFR Change from Screening (mL/min/1.73m ²)	-3.1±17.0 (230)	-1.0±16.4 (235)	-2.0±16.7 (465)

Pulmonary Embolism

- FDA was initially concerned about the potential for pulmonary embolism or occlusion
- No clear evidence that any PE occurred as a result of the sensor during the trial
 - Based on both clinical events and
 - Limited autopsy data

Effectiveness Results

Primary Effectiveness

- The rate of heart failure related (HFR) hospitalizations through 6 months
- Hospitalization events were reviewed by the Clinical Events Committee (CEC) and adjudicated in terms of being heart failure related vs. not related

Primary Effectiveness Results

	Treatment (270)		Control (280)		NBR p-value
	# Hosp	Hosp Rate (events/pt-6 months)	# Hosp	Hosp Rate (events/pt-6 months)	
Through 6 months	84	0.32	120	0.44	0.0002

The primary effectiveness endpoint appears to have been met.

Primary Effectiveness Question

- Primary effectiveness endpoint met
- Risk reduction is from 0.44 to 0.32 HFR hospitalization events/patient-6 months
- Absolute risk reduction is 0.12 HFR hospitalization events/patient-6 months
- The Panelists will be asked to discuss the clinical significance of this finding

Secondary Effectiveness

Endpoint	Treatment Group Outcome	Control Group Outcome	Absolute Difference in Outcome
Proportion Hospitalized for Heart Failure	20.4%	28.6%	8.2%
Days Alive Outside of Hospital	174.4 ± 31.1	172.1 ± 37.8	2.3
# of days Hospitalized	2.2	3.8	1.6
QOL (MLWHFQ)			
At 6 months	45.2 ± 26.4	50.6 ± 24.8	5.4
Change from baseline to 6 months	-10.6	-7.4	3.2

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Inclusion Criteria: Medical Therapy

- HF - low EF be on “stable optimally uptitrated medical therapy recommended according to current guidelines as standard of care for heart failure therapy in the US”.
 - An ACE-I, ARB at stable doses when ACE-I is not tolerated
 - Beta blocker, if tolerated, with a stable up-titrated dose
 - If ... intolerant to ACE-I, ARB, or beta blockers, documented evidence must be available. If intolerant to both ACE-1 and ARB, combination therapy with hydralazine and oral nitrate should be considered.

System PA Measurement: Treatment Group

- Standard of care HF management + HF management based on hemodynamic information obtained from the HF Pressure Measurement System.
- The Investigator or designee will review the PA pressure measurements from the home monitoring unit.
- Investigator or designee will be alerted by CardioMEMS, if those parameters are exceeded.
- If PA pressures are elevated, the Investigator or designee should make medication changes according to Appendix E.

Pulmonary artery mean pressure 10 – 25 mmHg considered “optivolemic”

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
Baseline Reference				
Mean±StdDev (mmHg) (N)	31.3±11.1 (265)	31.8±10.7 (272)	31.6±10.9 (537)	0.5562
Median	30.1	31.0	30.8	
(Min, Max)	(2.0, 61.6)	(3.7, 60.4)	(2.0, 61.6)	
Change from Baseline (AUC)				
Mean±StdDev (mmHg days) (N)	-155.7±1088 (265)	33.1±951.7 (272)	-60.1±1024 (537)	0.0077
Median (H-L estimate)	-7.2 (-115.6)	33.7 (47.4)	19.5 (-19.3)	
(Min, Max)	(-3121.1, 4782.5)	(-3694.0, 5725.7)	(-3694.0, 5725.7)	

Treatment if “optivolemic”: Appendix E

Baseline chronic aggressive therapy (low LVEF)

- ACEI /ARB or other vasodilator if ACE not tolerated to target dose
- Digoxin, diuretic, electrolyte replacement
- Consider spironolactone
- Nitrates to appropriate doses as tolerated
- Beta-blocker administration and/or uptitration according to guidelines when subject is not hypervolemic.

“Hypervolemic” Treatment Recommendation: Appendix E

- Add or increase or change diuretic
 - add thiazide diuretic or IV doses of loop diuretic
- Add or increase nitrates
- Start or re-educate in salt intake and fluid
- If poor perfusion: admission, IV agents, hemodynamics or if clinical evidence suggests need for IV diuretics, telemetry monitoring or the IV therapeutic agents
- Incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for HF

Sponsor Maximal Dose Definition

<i>Medication</i>	<i>Maximal Dose Forced Titration Dose</i>	<i>Dose at Baseline Mean±SD mg (N=Pts.)</i>	<i>Dose at 6 Months Mean±SD mg (N=Pts.)</i>
ACE/ARB	40 mg 16.6 mg	20.83±19.66 (N=427)	22.85±22.36 (N=416)
Beta Blocker	50 mg 41.8 mg	30.14±25.42 (N=499)	32.44±26.66 (N=482)
Aldosterone Antagonist	50 mg 26 mg	30.60±21.31 (N=231)	32.14±23.18 (N=254)
Nitrate	120 mg 76 mg	58.96±35.35 (N=120)	64.35±48.16 (N=178)
Hydralazine	300 mg 142.5 mg	121.45±92.46 (N=69)	138.73±100.55 (N=103)

Baseline Medical Therapy

HF Medication	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
ACE/ARB	205 (75.9%)	222 (79.3%)	427 (77.6%)	0.3584
Beta Blocker	243 (90.0%)	256 (91.4%)	499 (90.7%)	0.6595
Aldosterone Antagonist	117 (43.3%)	114 (40.7%)	231 (42.0%)	0.5463
Nitrate	64 (23.7%)	56 (20.0%)	120 (21.8%)	0.3035
Hydralazine	36 (13.3%)	33 (11.8%)	69 (12.5%)	0.6084
Diuretic-Loop	248 (91.9%)	258 (92.1%)	506 (92.0%)	>0.9999
Diuretic-Thiazide- Standing	30 (11.1%)	35 (12.5%)	65 (11.8%)	0.6922
Diuretic-Thiazide-PRN	20 (7.4%)	18 (6.4%)	38 (6.9%)	0.7374

Fraction of Maximal Dose: Change from Baseline to 6 months

	Baseline Mean±SD		6 Months Mean±SD		Change from Baseline Mean		
Medication	Treatment (n=270)	Control (n=280)	Treatment (n=270)	Control (n=280)	Treatment (n=270)	Control (n=280)	p
ACE/ARB	0.52±0.49 (n=189)	0.54±0.51 (n=203)	0.62±0.61 (n=189)	0.54±0.52 (n=203)	0.11	0.00	0.0042
Beta Blocker	0.59±0.44 (n=228)	0.63±0.57 (n=240)	0.65±0.49 (n=228)	0.64±0.57 (n=240)	0.07	0.01	0.0481

Medical Therapy at 6 Months

HF Medication	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
ACE/ARB	203 (75.2%)	213 (76.1%)	416 (75.6%)	0.8428
Beta Blocker	236 (87.4%)	246 (87.9%)	482 (87.6%)	0.8975
Aldosterone Antagonist	130 (48.1%)	124 (44.3%)	254 (46.2%)	0.3926
Nitrate	113 (41.9%)	65 (23.2%)	178 (32.4%)	<0.0001
Hydralazine	61 (22.6%)	42 (15.0%)	103 (18.7%)	0.0285
Diuretic-Loop	239 (88.5%)	251 (89.6%)	490 (89.1%)	0.6840
Diuretic-Thiazide-Standing	53 (19.6%)	41 (14.6%)	94 (17.1%)	0.1407
Diuretic-Thiazide-PRN	33 (12.2%)	30 (10.7%)	63 (11.5%)	0.5948

Summary

- % pts on ACEI/ARB low
- % target doses low for ACEI/ARB and BB

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Post-Approval Study Considerations

Shaokui Wei, MD, MPH
Division of Epidemiology
Office of Surveillance and Biometrics

Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating **a reasonable assurance of safety and effectiveness** and an appropriate risk/benefit balance

Need for Post-Approval Studies

- Gather postmarket information
 - Long-term performance including effects of re-treatments & device changes
 - Real-world device performance (patients and clinicians)
 - Effectiveness of training programs
 - Sub-group performance
 - Outcomes of concern (safety and effectiveness)
- Account for Panel recommendations

Overview of Sponsor's Proposal

Study Design	A prospective, multi-center, open-label trial conducted in the US to evaluate the long term safety and effectiveness of the Champion System
Safety Hypotheses	<ul style="list-style-type: none">■ Freedom from device/system related complications at 6 months < 80%■ Freedom from pressure sensor failure at 6 month < 90%.
Effectiveness Hypothesis	12 month HFR hospitalization rate after device implant \geq year prior to implant
Population	all subjects who sign the informed consent form and satisfy the inclusion/exclusion criteria at the baseline visit with a maximum of 967 patients.
Follow-up	Every 6-months through two years

Assessment of Sponsor's Proposal

1. Whether 6-months and 12- months are the appropriate length of follow-up over which the safety and effectiveness hypothesis should be tested.
2. Whether the historical control HFR hospitalization rate in the year prior to CHAMPION is the appropriate comparison for effectiveness evaluation.
3. Whether there are other effectiveness endpoints that should be included as secondary endpoints.
4. Whether a specific effort should be made to study device effectiveness in women with heart failure.

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Study Protocol

- Sponsor was aware of the pressure readings from the sensor
- Protocol allowed sponsor to contact sites regarding sensor pressure readings
- “The Investigator or designee will review the PA pressure measurements from the home monitoring unit. Alert limits are automatically set as described in Appendix E. The Investigator or designee will be alerted by CardioMEMS, if those parameters are exceeded. If the PA pressures are elevated, the Investigator or designee should make medication changes according to the recommendations in Appendix E.”¹

Trial Conduct

- Sponsor was aware of the randomization assignment
- Sponsor contacted clinical sites on a regular basis
- Email communications
 - Were patient-specific
 - Included recommendations for medical therapy
 - often quite specific
 - Tailored to meet individual patients' needs
 - Included recommendations for diagnostic testing
 - Were for Treatment group subjects only

Communication Consistent with FDA's Expectations

- On 11-16-2009, a CardioMEMS nurse wrote *“Just wanted to make sure you are aware of upward trend of PA pressures for [specific subject]. Do you know if [site investigator] plans on any changes to his medications?”*

Recommendations based on prior subject-specific responses

On 8-21-2009 , a CardioMEMS nurse wrote “*I wanted to alert you to [specific subject]’s increase in pressures over the past week with a mean of 42 today. She responded nicely to extra Lasix back in May. Would you consider this again?*”

Recommendations regarding the discontinuation of disadvantageous medications

On 12-29-2008, a CardioMEMS nurse wrote “*I wanted to alert you of an increasing trend in the mean of [specific subject]. Although his mean pressure trend remains relatively flat, his pressures have an upward trend. We are seeing several patients in the trial experience post-holiday rise in pressures most likely due to dietary indiscretion and medication noncompliance. Do you think this patient would benefit from a few days of increase diuretic until his pressures return to baseline? I also noticed that this patient is on Metformin in the face of renal insufficiency (SCr 1.4) which may be contributing to difficulty in managing his volume status.*”

Suggested medications not listed in Appendix E of the protocol

On 2-4-2009, a CardioMEMS nurse wrote

- 1. PCWP 17 with PAM at 49 at implant – consider increasing Lasix mg dose or frequency. If not responding well to Lasix consider switching to Demadex and/or adding a PRN Thiazide*
- 2. Add Hydralazine/Nitrates to current regimen and up-titrate to optimal dose as tolerated. Once optimized on H/N and pressures still elevated – consider pulmonary vasodilator i.e. Sildenafil”*

Recommended evaluating Treatment group subjects for sleep disorders

On 10-30-2008, a CardioMEMS nurse wrote recommendations that include *“PCWP 14 suggests increased volume- Consider increasing Lasix to 40mg BID or switching to Demadex if bioavailability a concern with Lasix. Consider using PRN Thiazide to facilitate diuresis. Up-titrate Diovan to optimal dose as tolerated (160mg BID). Add Hydralazine and Nitrates to current regimen uptitrating as tolerated. Evaluate patient's current compliance with treatment of his Obstructive Sleep Apnea. Consider re-evaluation of patient's Sleep Breathing Disorder diagnosis (OSA vs Central Sleep Apnea) and options for treatment.”*

Suggested the use of outpatient IV Therapy

On 12-12-2008, a CardioMEMS nurse wrote “*What is your plan for management of [specific subject]? Implant hemodynamics (PA 68/41(52) PCWP 30 CO 1.5 PVR 14.67) suggested increased volume with a PCWP 30 in addition to PAH with a PVR 14.67. Addition of Ismo 40mg QD on 10/2/08 appears to have helped with a decrease in PAM from 43 to 31. She is on maximum medical therapy (ARB, BB, Nitrate, Aldactone, Digoxin, Diuretic) at this point. Would you consider challenging her with Sildenafil in addition to adjusting her diuretic regimen by switching to Demadex or possibly using outpatient IV diuretics?*”

Suggested the use of outpatient IV Therapy #2

- On 11-4-2009, a CardioMEMS nurse wrote “*I just wanted to make sure you and Dr. [site investigator] are aware of the elevated PA pressures for [specific subject]. There may be some benefit from an increase in her Hydralazine/Nitrate or, as we have discussed before, and increase in diuretic. If Dr. [site investigator] would like to bring the patient into the clinic for IV diuretics and transportation is an issue for her please give me a call.*”

Suggested the use of outpatient Inotropes

- On 7-29-2009, a CardioMEMS nurse wrote “*I appreciate the update. It sounds like he is getting more difficult to manage, especially with his hypotension. I also noticed that his HR has been up into the upper 80's where it has been running consistently in the 70's. ... I know that in the past he received intermittent outpatient inotropes. Has there been any consideration in starting him back on this?*”

Treatment Recommendation Accepted

- On 2-10-2009, a CardioMEMS nurse wrote “1. *PCWP 36 with PAM 42 at implant- consider increasing Lasix mg dose or frequency.*”
Several other recommendations were also made.
- Later that day, the site investigator wrote “*Great. I would like to see these regularly. Go ahead and have pt take extra 40mg of lasix daily at 2 pm for 5 days*”

Working Together to Manage Patients

- On 5-9-2008, a CardioMEMS nurse wrote *“Once I get a current update from you regarding these cases, I can make some recommendations regarding medical management. I look forward to hearing from you and working together to manage these patients. Feel free to call me anytime if you have questions.”*

Working Together to Manage Patients #2

- On 5-7-2008, a CardioMEMS nurse wrote *“Feel free to call me anytime if you have questions regarding the medical management of your treatment arm patients. I look forward to working with you to optimize their medical therapy.”*

Other Recommendations

- On 12-26-2008, a CardioMEMS nurse wrote “*I wanted to alert you that [specific subject]’s mean pressure went from 27 on 12/24 to 53 on 12/26. Do you think this warrents her to take an extra dose of diuretics today? It is the holidays and we expect pressures to increase, but we still want to prevent her from going to the hospital.*”

Medical Therapy Recommendations from National Principal Investigators

- On 11-16-2007, one of the national PIs sent the following email to CardioMEMS after talking with the principal investigator at a specific site. *“I spoke with [the site principal investigator] this morning. We had a very collegial and productive discussion about hemodynamic monitoring, in general, and his patients, in particular. It sounds like patient #2 is very ill and will likely be made DNR. Patient #3 has had persistent elevation in her PA pressures, despite escalation of diuretic dose. Following [CardioMEMS employee]’s conversation with [the site principal investigator] yesterday, he increased the furosemide dose from 80 mg bid to 120 mg bid (the patient was previously [prior to 10/25] on 40 mg bid). The patient does not have any clinical signs of extra-cellular fluid volume excess. The patient does, in fact, have substantial mitral regurgitation. I suggested that he consider starting a long acting nitrate and letting me know what happens; we may need to back off of the diuretic, if the nitrate works. I also thanked him for his great and ongoing contribution to the study.”*

Trial Conduct Concerns

- Sponsor & National PIs made specific treatment recommendations for Treatment group only
- Level of interaction between sponsor and clinical investigators inconsistent with FDA's expectations
- FDA concerned these actions may bias results
- FDA believes measures taken by sponsor would not be duplicated in post-market setting

Trial Conduct Concerns Summary

- Substantial therapy recommendations were made only for the treatment group subjects
- FDA is concerned that the observed treatment effect may not be due solely to the device
- Given the potential bias introduced by study conduct, FDA is concerned that we cannot make an accurate risk:benefit determination for this device

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Some Overarching Statistical Considerations

Gregory Campbell, PhD
Director, Division of Biostatistics
CDRH

Diagnostic Devices

There are fundamentally two ways to evaluate diagnostic devices.

1. Diagnostic performance study

Usually there is a “gold standard” for truth and the performance of the diagnostic device is compared the “gold standard”.

2. Clinical outcome study

The diagnostic device is studied according to whether it has an effect on clinical outcomes.

Diagnostic Clinical Outcome Studies

- These studies can be difficult to do. They can pose challenges to those who are only familiar with therapeutic clinical trials.
- It is the information that is provided by the diagnostic test that is under study. In particular, does that information make a clinical difference?
- In most such studies it is usually very helpful to see if the physicians who had that information used it or found it helpful. Namely, at the individual physician level, did that information make a difference or was it ignored?

Bias Reduction in Randomized Clinical Trials

- Fundamental idea: Control for all other possible variables, plan to treat both of the arms exactly the same way and then randomly assign subjects to one of the two arms. If so, the only difference between the two arms is the effect of the investigational medical intervention (in this case the information from CardioMEMS).

Bias Reduction in Randomized Clinical Trials

- If the two arms are treated differently this can introduce a potentially large bias. (In CHAMPION, the two arms are treated very differently by recommendations by entities outside the clinical site.)
- In general, failure to mask (blind) the subjects, the investigators or the third-party evaluators introduces a bias.
 - Only subjects were blinded in this study

Challenge of Evaluating Diagnostic Devices in Clinical Outcome Studies

- Impossible to mask the treating physicians from the output of the diagnostic device. However, patient-specific recommendations that the sponsor provided to the clinical sites are problematic. In addition, the sponsor has not remained masked (blinded) and has made differential patient-specific recommendations in only one of the two arms.
- Desirable to have an endpoint that cannot be directly and easily influenced by knowledge of which group a subject is in. That is not the case for this PMA, where the primary effectiveness endpoint is HFR hospitalizations.

Planned Objective

- Evaluate the effectiveness of the CardioMEMS device in reducing HFR hospitalizations in subjects
 - Diagnostic outcome study
 - Potential bias if physician behavior is affected other than through device information
 - Protocol guidelines which are provided in Appendix E help to minimize this bias

“Extra Interventions”

- Reminders to investigators in the one arm that could keep Treatment patients out of the hospital.
- Close monitoring only of patients in the Treatment arm by CardioMEMS HF nurses, resulting in differential patient-specific recommendations.
- Consultations between clinical sites and National Principal Investigators regarding treatment strategies for particular patients only in the Treatment arm.
- Recommendations for treatment strategies that could keep only patients in Treatment arm from HFR hospitalization.

Possible Causal Inferences

- Incorporation of hemodynamic information from CardioMEMS device into physician decisions reduces HFR hospitalizations.
- CardioMEMS Nurses and National Principal Investigators made differential patient-specific recommendations (only in the Treatment arm) to the clinical sites that resulted in a reduction in HFR hospitalizations

The Dilemma

- The effect of this study is confounded.
- It is the confounding of the diagnostic information and the “Extra Interventions”
- The possible bias from this confounding is of serious concern here and, given the sensitivity analyses presented earlier, this bias could have produced some or all of the significant effectiveness results seen in this trial.

A Thought Experiment

- Consider a randomized controlled clinical trial with two arms. Suppose the one arm is Standard of Care and the other is Standard of Care plus “Extra Interventions” (but no diagnostic device) in the form of the oversight of a clinical support team of nurses at a central location who provide advice upon request to prevent hospitalizations and who also make contact with the investigators at times to suggest changes in therapy.
- It would not be surprising to see a difference in the two arms.

Intended Use

- How is the device intended to be used?
- The proposed indications for use statement put forth by the sponsor does not specify an automated or personalized effort by the sponsor for the device. If the intention of the sponsor is to use the device as the major part of a Clinical Decision Support System (CDSS), then that system would be what would be evaluated as part of the trial. The protocol then would include, for example, the algorithm that specified the automated e-mails to the physician, the content of those e-mails and a more tailored approach by CardioMEMS nurses and others that makes patient-specific treatment suggestions.
- This study did not evaluate such a proposed system.

Conclusions

- Confounding of planned intervention (use of CardioMEMS information by the physician) and “extra interventions” (differential patient-specific treatment recommendations) renders interpretation of this trial problematic.
 - Which intervention caused the observed outcome?
- The CHAMPION trial does not provide an unbiased estimate of the effect of the device. It is not clear what if any effect in the study is due to the device itself. Further, the effect of the device in a real-world setting (if this device were to be approved) is unknown.

Thank you.

Backup Slides

Statistics Back Up Slides

Primary Effectiveness Endpoint

- Rate of heart failure related hospitalizations at 6-month

$$H_a: \mu (\text{TREATMENT}) \neq \mu (\text{CONTROL})$$

- Negative binomial regression was used by sponsor:

	Treatment (270)	Control (280)
# of event	84	120
Events/patient-6-month	0.32	0.44

- Estimate of the treatment effect (sponsor's option with offset)
 - Point estimate of IRR=1.378, 95% CI: (1.189, 1.599)
 - IRR: incidence rate ratio (cont vs. Trt), IRR >1 indicating treatment benefit

Sensitivity Analysis: # of hosp

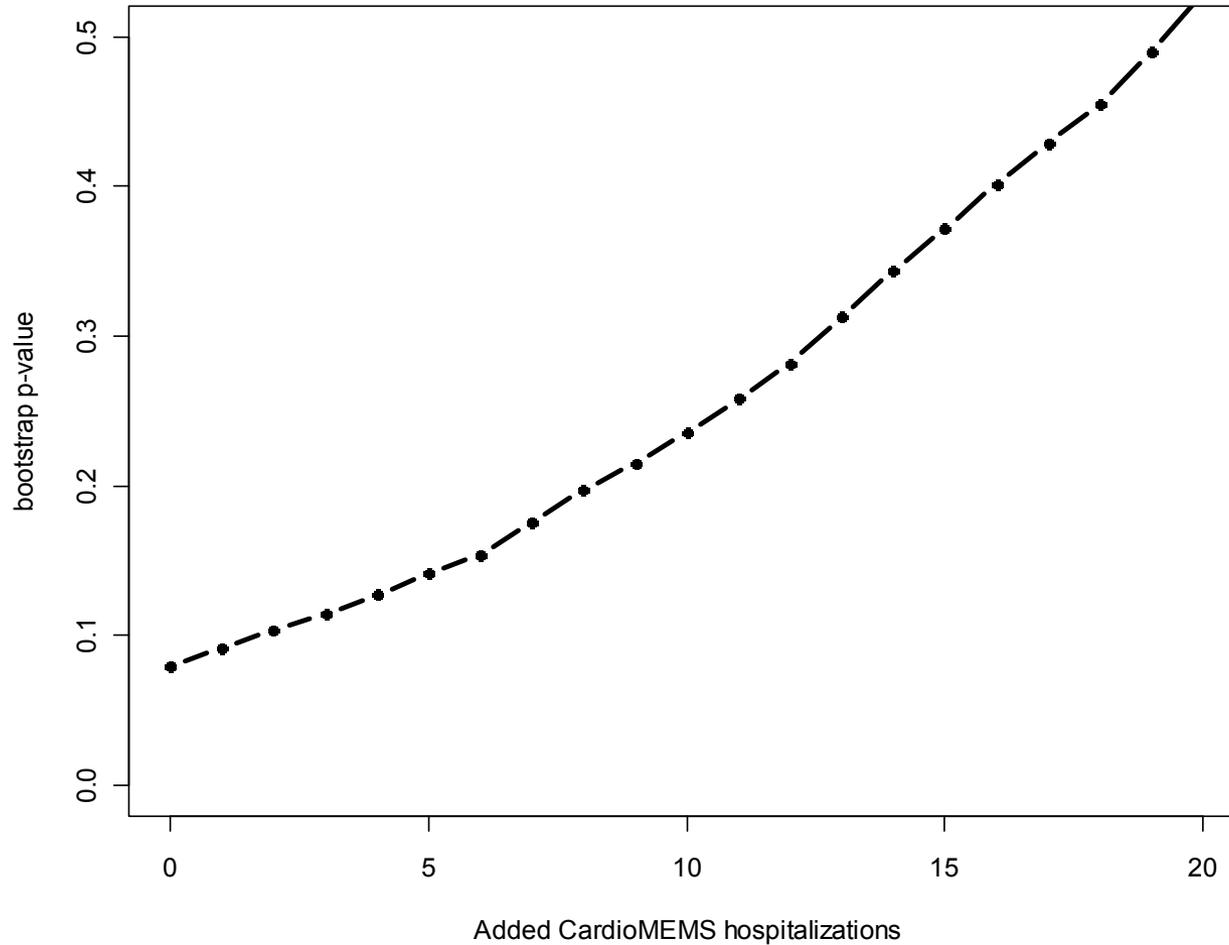
Add additional hosp in treatment arm, under sponsor's model	P-value for treatment
10	0.03
12	0.044
12	0.052
12	0.025
13	0.062
13	0.081
15	0.087

Non-parametric analysis of # hosp.

With Bootstrap approach:

- Event rate of treatment arm
 - Point estimate: 0.32, 95% CI: (0.23, 0.41)
- Event rate of control arm
 - Point estimate: 0.44, 95% CI: (0.35, 0.54)
- Incidence rate ratio
 - Point estimate: 1.42, 95% CI: (0.98, 1.99)
- P-value for treatment effect: 0.07

P-values for bootstrap with added hospitalizations



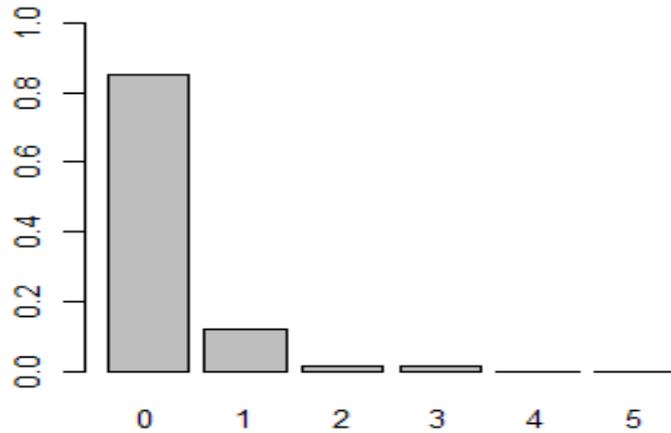
Model Comparison

Model	Scaled Deviance	BIC (smaller=better)	P-value for treatment
Sponsor's	0.4172		0.0002
Basic Poisson	1.1659	958.85	0.0227
Scaled Poisson	1	824.17	0.0348
Zero Inflated Poisson	0.997	890	0.0107 (zero-model)
Basic Negative Binomial	0.6838	907	0.1137
Scaled Negative Binomial	1	907	0.0557
Nonparametric (bootstrap)	NA	NA	0.070 (2*0.035)

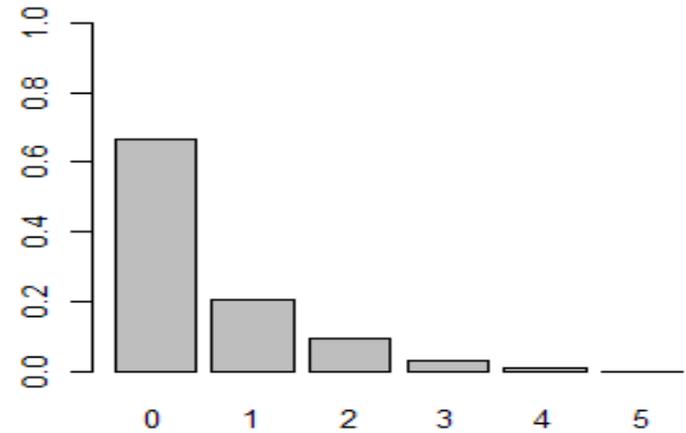
Model Summary

Model	Point estimate of IRR, 95% CI	P-value for treatment
Sponsor's negative binomial model	1.36, (1.172, 1.583)	0.0002
Basic Poisson	1.38, (1.046, 1.827)	0.0227
Variance-Scaled Poisson	1.38, (1.023, 1.869)	0.0348
Zero-Inflated Poisson Zero-Inflated NB		0.0107 for zero- model
Basic Negative Binomial	1.34, (0.932, 1.941)	0.1137
Variance-Scaled Negative Binomial	1.34, (0.993, 1.822)	0.0557
Nonparametric (bootstrap)	1.42, (0.98, 1.99)	0.070 (2*0.035)

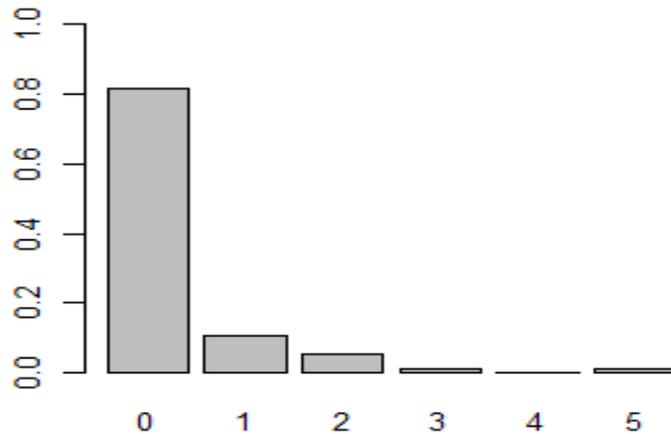
Relative freq. of 4 subgroups: # of Hosp.



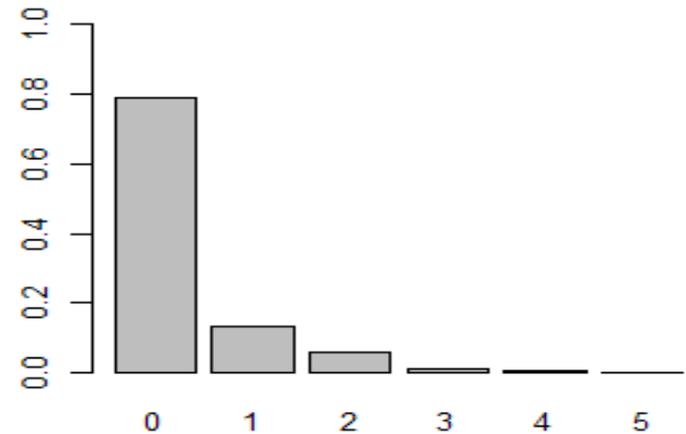
Female Control



Male Control



Female Treated

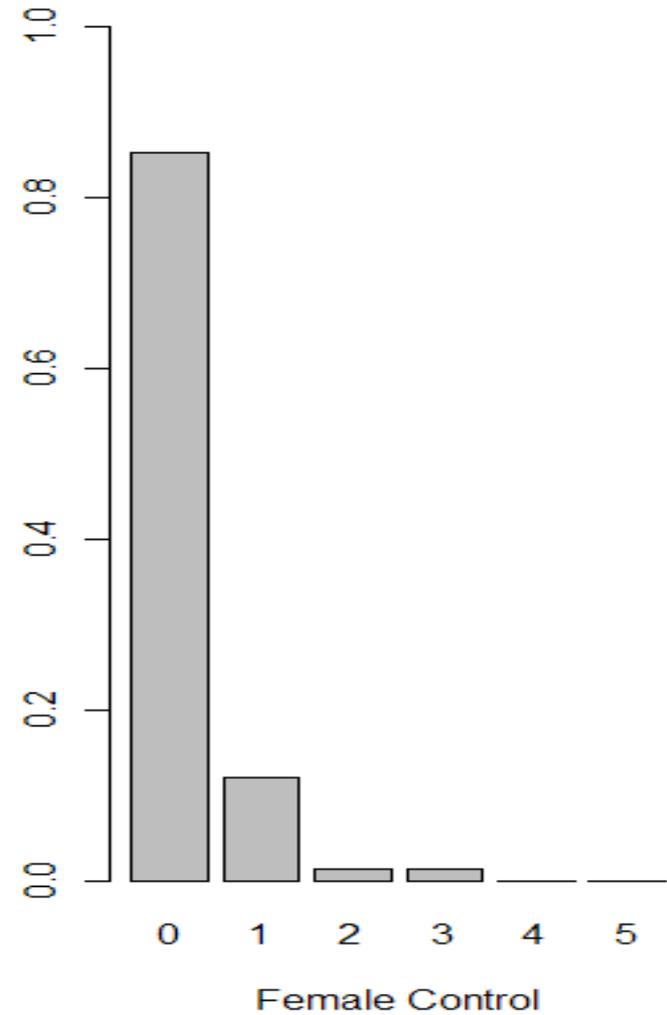
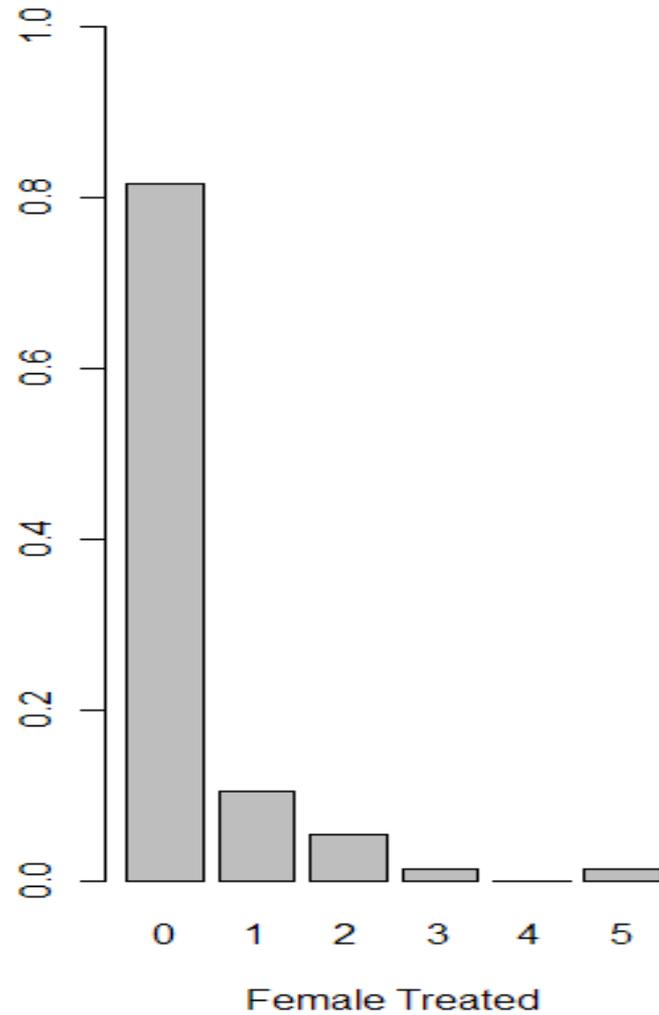


Male Treated

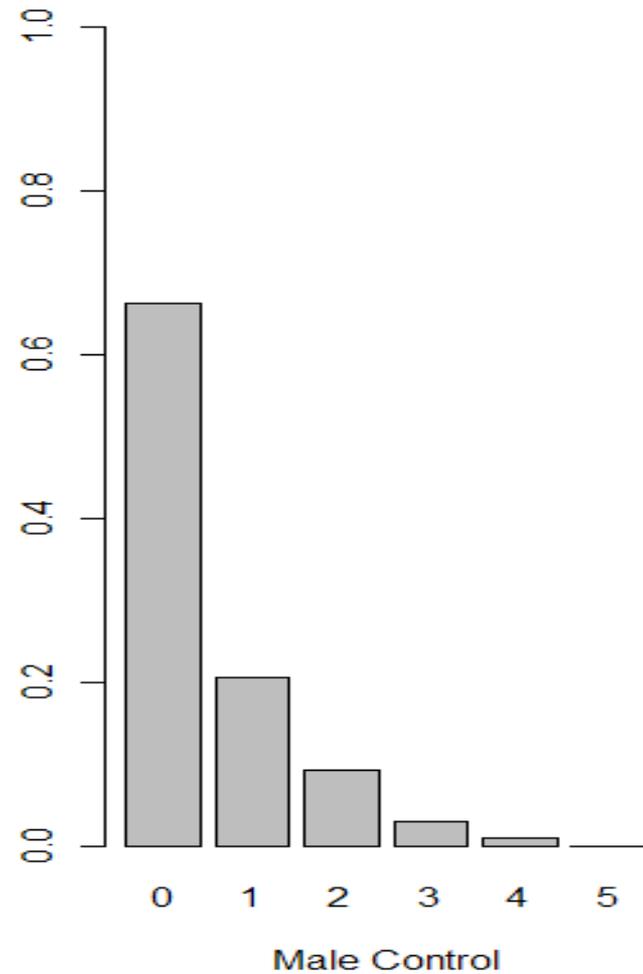
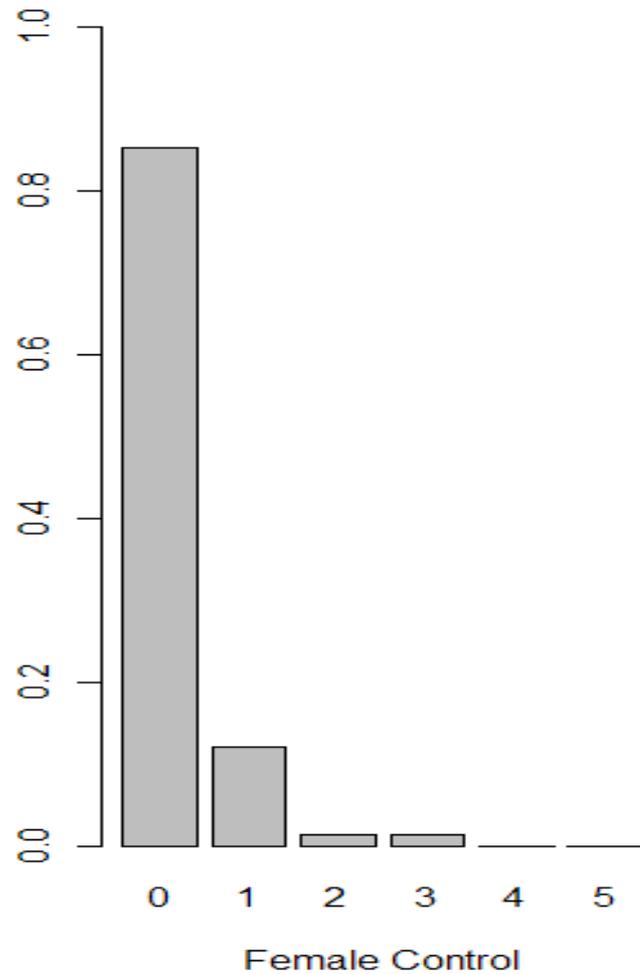
Distribution of # of Hosp.

# of Hosp	0	1	2	3	4	5
Female, Trt 76	62 (.816=62/76)	8 (.105)	4 (.053)	1 (.013)	0 (0)	1 (.013)
female, Cont. 75	64 (.853)	9 (.12)	1 (.013)	1 (.013)	0 (0)	0 (0)
Male, Trt. 194	153 (.789)	26 (.134)	12 (.062)	2 (.013)	1 (.005)	0 (0)
Male, Cont. 205	136 (.663)	42 (.205)	19 (.093)	6 (.029)	2 (.009)	0 (0)
Overall	415 (.755)	85 (.155)	36 (.065)	10 (.018)	3 (.005)	1 (.0018)

Female Trt. Vs. Female Cont.



Female Cont. Vs. Male Cont.



Overall Distribution: Poisson?

	0	1	2	3	4	5
obs.	415 (.755)	85 (.155)	36 (.065)	10 (.018)	3 (.0055)	1 (.0018)
Fitted ($\mu=.371$)	380 (.690)	141 (.256)	26 (.047)	3 (.0587)	3 .0055	0 0

- **Observed mean: 0.371, variance: 0.57**
- **Pearson chi-square: 1.8825, p-value=0.17,**
- **can't reject Poisson distribution**

Break down by treatment: Poisson Distribution?

	0	1	2	3	4	5
Trt. Fitted	.733	.228	.035	.0037	.0003	0
(obs.)	(.796)	(.126)	(.059)	(.011)	(.0037)	(.0037)
Obs. Freq.	215	34	16	3	1	1
Cont.(Fitted)	.651	.279	.059	.0085	.0009	0
(obs.)	(.714)	(.182)	(.071)	(.025)	.0071	(0)
Obs. Freq.	200	51	20	7	2	0

	mean	variance
Trt.	0.3111	0.5199
Cont.	0.4286	0.6257

Follow-up Time at 6-month

- Descriptive statistics for 6-month follow-up time

	All: mean	Hospitalized: mean
Male Trt.	176.68 (194)	168.34 (41)
Male Cont.	177.08 (205)	176.38(69)
Female Trt.	176.44 (76)	158.85 (14)
Female Cont.	172.74 (75)	167.18 (11)

- Control pts: Male pts had longer follow-up time than female

Study Duration Follow-up Time

- Descriptive statistics for study duration

	Mean Follow-up time	Mean # Hospitalized
Male Trt. (194)	465.39	0.588
Male Cont. (205)	451.18	1.044
Female Trt. (76)	445.03	0.579
Female Cont. (75)	446.87	0.533

- Control pts: Male pts had more events although shorter follow-up

Gender Difference: significant predictors

Significant predictors for # of hosp.

predictor	male	female	P-value
Age	62.4	59.5	.0359
Diabetes	49%	48%	.9462
AF	51%	33%	.0003
Heart rate	72.1	74.5	.1353
Baseline BMI	30.4	32.2	.0227
Cardiac Output	4.63	4.21	0.0025
Cardiac Index	2.29	2.34	0.4986
ACE_ARB_use	80.2%	75.5%	0.2758

Model with Covariates: gender issue

- Y: # of hosp.
- X: all important covariates
Trt, Age, Diabete, AF, Heart_rate, screening_GFR, PVR, Beta_blocker_dose, systolic_function, BMI, systolic_bp, screening_creatinine, BUN, cardiac_output, cardiac_index, ACE_ARB_use, ischemic_cardiomyopa, ejection_fraction, gender, Trt*gender
- Poisson regression with variance rescaled, follow-up time as offset variable
- Result:
 - Trt is significant
 - significant interaction of Trt*gender

Model with Significant Covariates

- Y: # of hosp.
- X: all important covariates
 - Trt, Age, Diabete, AF, Heart_rate, ACE_ARB_use, gender, Trt*gender
- Poisson regression with variance rescaled, follow-up time as offset variable
- Result:
 - Trt is significant
 - significant interaction of Trt*gender

Secondary Endpoint 2: tipping point analysis

- 3 more pts had event in treatment arm, non-significant result

	Treatment (270)	Control (280)	p-value
# of pts have event	57 (21.1%)	80 (28.6%)	0.0486
# of pts have event	58 (21.5%)	80 (28.6%)	0.0617

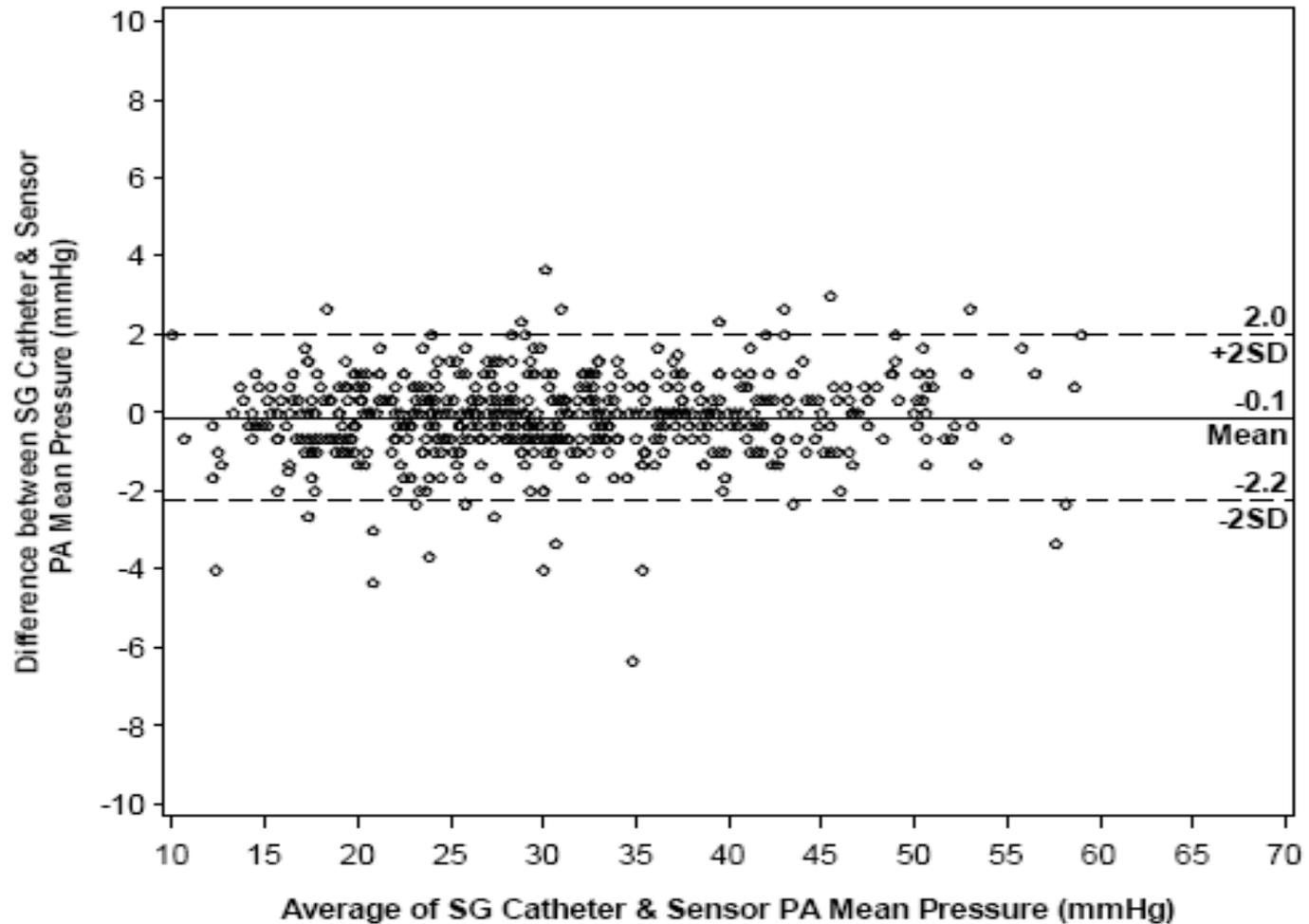
Secondary Endpoint 2: tipping point analysis

- 3 less pts had event in control arm, non-significant result

	Treatment (270)	Control (280)	p-value
# of pts have event	55 (20.4%)	78 (27.9%)	0.046
# of pts have event	55 (20.4%)	77 (27.5%)	0.058

Sensor Performance: Baseline

- Baseline Bland-Altman plot: mean of 0.1mmHg



Analysis Population

- Intent-to-Treat Population (ITT): all patients who were randomized (after successful implantation) into the study, regardless of study completion status. Effectiveness endpoints were analyzed on the ITT population.
- Per Protocol Population (PP): subjects who completed 6 months of the study without major protocol violations. Effectiveness endpoints were analyzed on the PP population also, as part of the supplementary analyses
- Safety Population: patients who received a sensor implant or underwent the implant procedure but were never implanted, regardless of study completion status. Primary safety endpoint analyses were performed on the safety population.

Interim Analysis Result

- When 275 pts had 6-month follow-up data, analyses of primary endpoints were conducted at the significance level of 0.005
- For the two primary safety endpoints, the p-values were less than 0.0001, data crossed the stopping boundary
- For the primary effectiveness endpoint, the p-value was larger than the stopping criterion of 0.005.
- The trial was not stopped early

Secondary Endpoint 1

- Change from baseline in pulmonary artery pressures, t-test

	Treatment (265)	Control (272)	p-value
Mean change (over 6-month)	-155.7mmHgdays	33.1mmHgdays	0.0077
STD	1088	951	

- This secondary effectiveness endpoint was met.

Secondary Endpoint 2

- Proportion of subjects hospitalized for heart failure
- exact test was used

	Treatment (270)	Control (280)	p-value
# of pts have event	55 (20.4%)	80 (28.6%)	0.0292

- This secondary endpoint was met.

Secondary Endpoint 3

- Days alive outside of the hospital
- Wilcoxon rank sum test

	Treatment (270)	Control (280)	p-value
Days alive Out H.	174.3±31.1	172.1±37.8	0.028 (after adjusted for duration)
Adjusted	177.3±9.31	175.8±12.59	

- Adjustment: $180 \times \text{Days Alive Outside Hospital} / \text{Subject Duration}$, pre-specified
- This secondary endpoint was met.

Secondary Endpoint 4

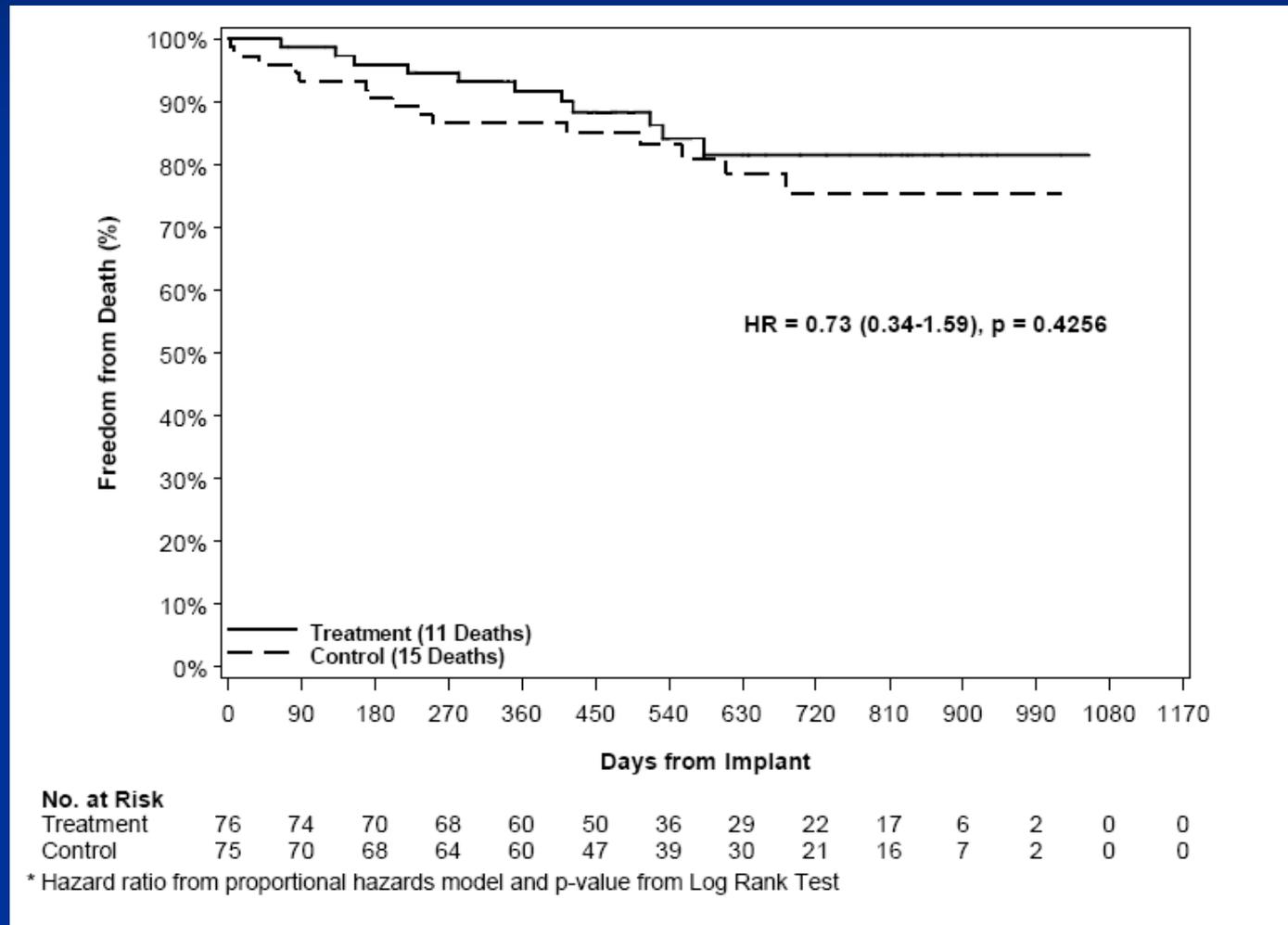
- Quality of Life- Minnesota Living with Heart Failure Questionnaire (MLHFQ) at 6-month, t-test

	Treatment (229)	Control (236)	p-value
Mean score	45.2 ± 26.4	50.6 ± 24.8	0.0236

- This secondary endpoint was met based on available data.
- Missing data for this variable: 41 (15%) out of 270 test patients and 44 (15.7%) out of 280 control patients did not have MLHFQ at 6-month. Last observation carried forward (LOCF) method was used to impute missing values for those 85 patients. This endpoint met the pre-specified criteria based on the LOCF imputation approach with a p-value of 0.0054.

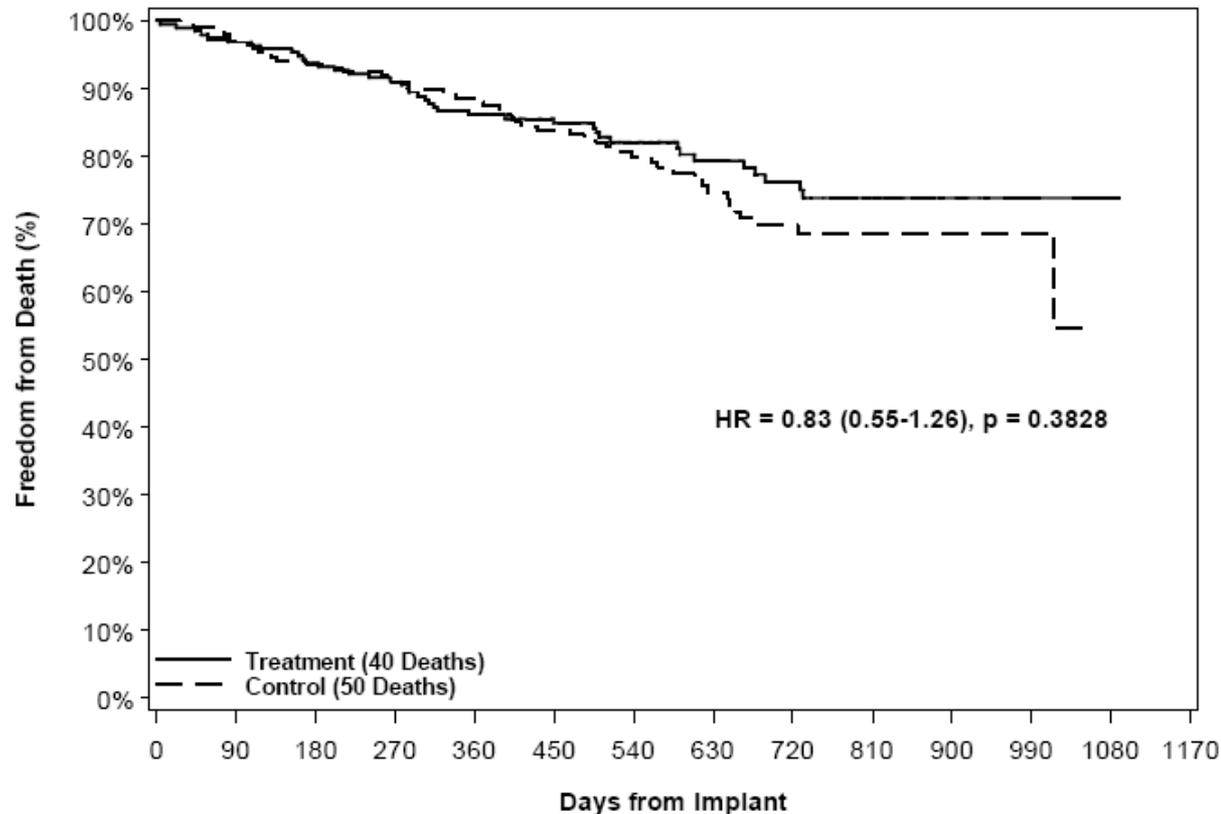
Female Survival Analysis

- There was no statistically significant difference in survival between the treatment and control groups for female



Male Survival Analysis

- There was no statistically significant difference in survival between the treatment and control groups for male



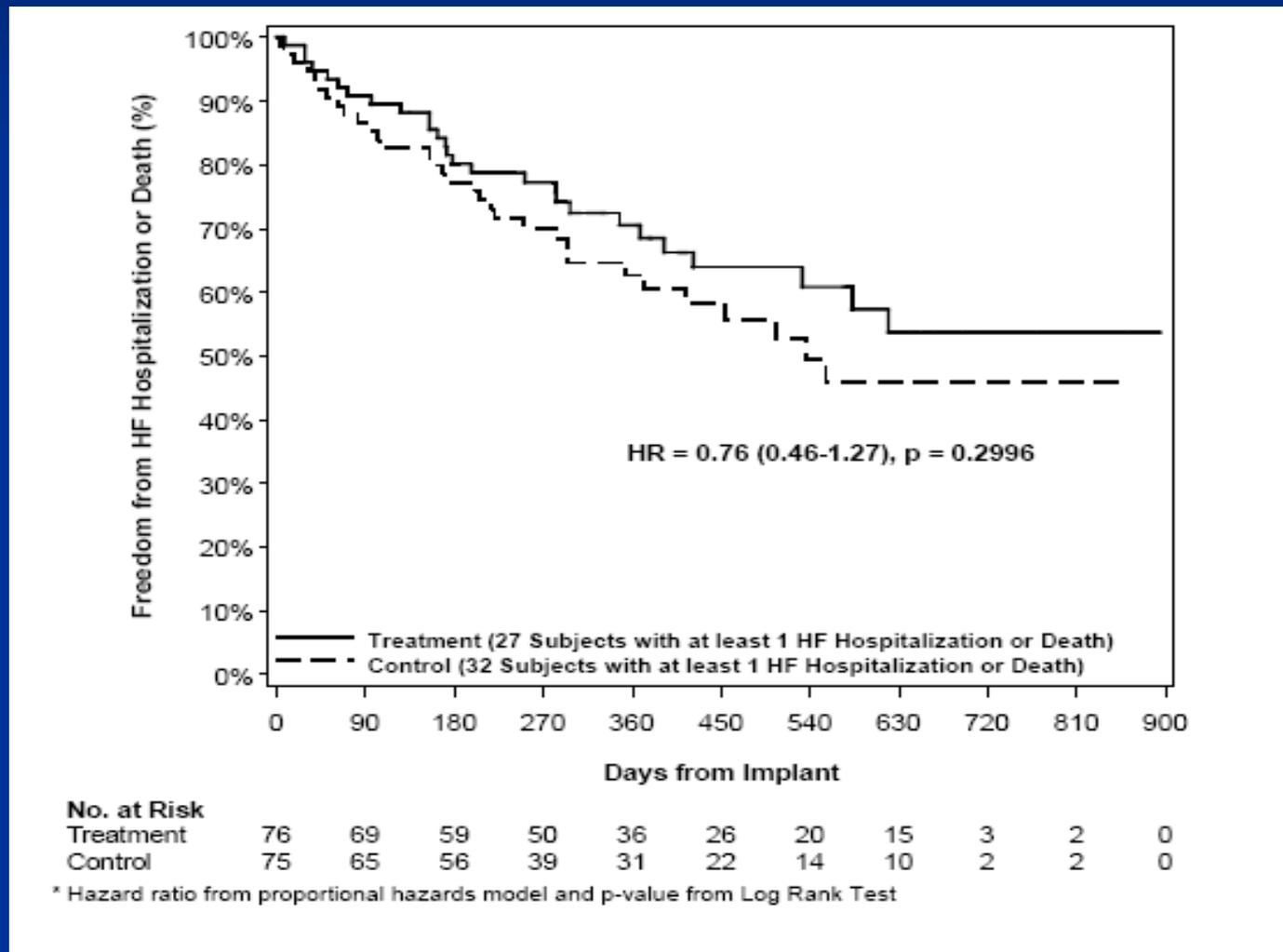
No. at Risk

Treatment	194	188	176	168	152	130	106	84	64	45	17	3	1	0
Control	205	197	186	177	163	139	107	78	52	32	13	5	0	0

* Hazard ratio from proportional hazards model and p-value from Log Rank Test

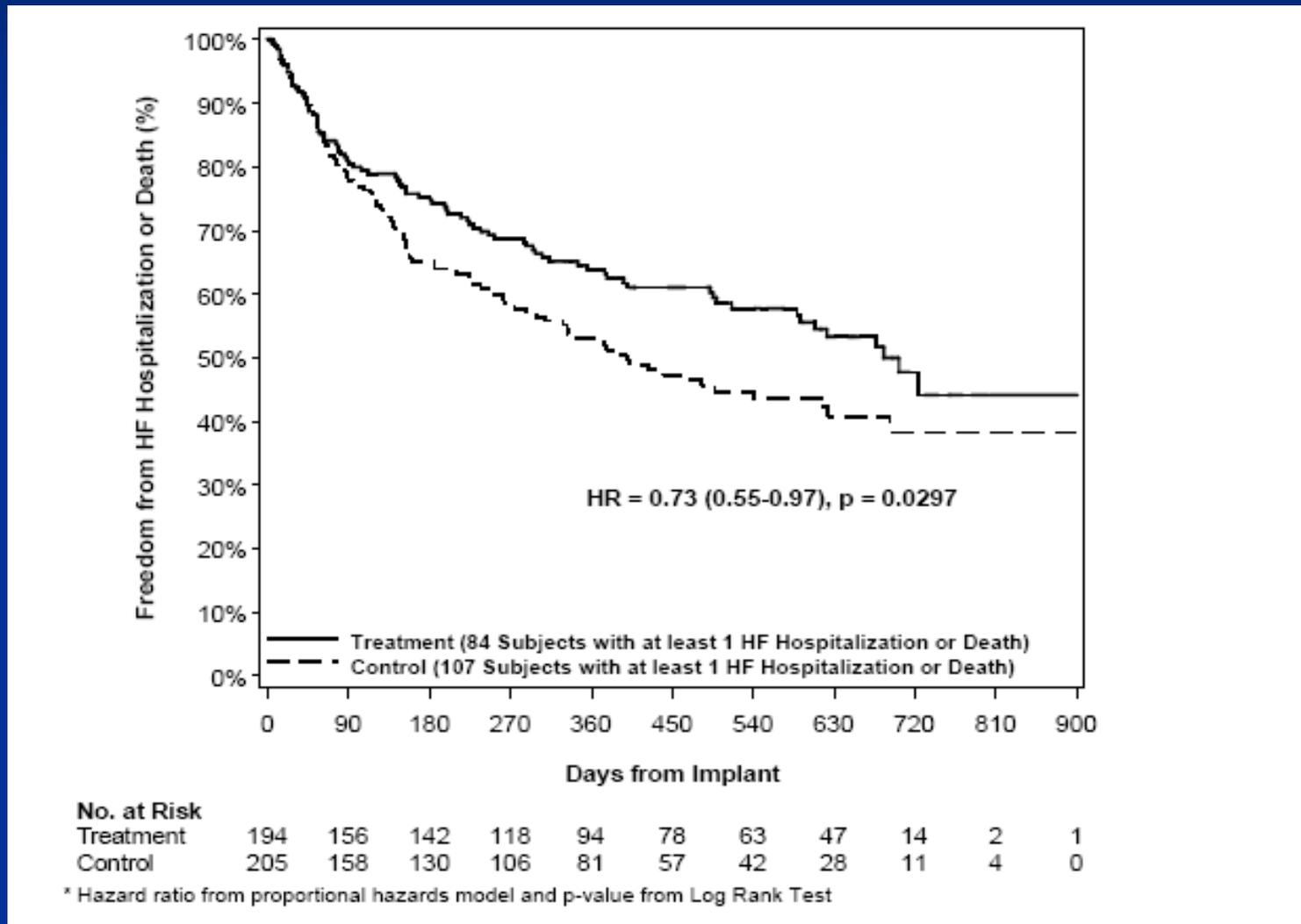
HFR Hospitalization-Free Survival: Female

- There is no significant benefit in reducing time to death or first HFR hospitalization for female



HFR Hospitalization-Free Survival: male

- There is significant benefit in reducing time to death or first HFR hospitalization for male



Brockman Back-up Slides

Anticipated Adverse Events Through 30 Days

	Treatment (270)		Control (280)		All Patients (550)	
	Subjects	Events	Subjects	Events	Subjects	Events
All Subjects with an Event	38 (14.1%)	47	31 (11.1%)	34	69 (12.5%)	81

Procedure-Related Adverse Events

- Separate analysis from “Anticipated Adverse Events”
- Sponsor reported seven (7) procedure-related AEs
 - AF, cardiogenic shock, fever, groin hematoma, groin pain, hemoptysis and prolonged hospitalization to restart warfarin
 - Four (4) events overlapped with “Anticipated AE” analysis
- Combined procedure and 30-day anticipated AE event rate is 13.1% (confidence intervals: 10.44% to 16.27%)

Procedure Related Adverse Events

Procedure Related	Description	Treatment	Outcome
Atrial fibrillation	History of Atrial Fibrillation. One day post-procedure developed rapid Atrial Fibrillation.	<ul style="list-style-type: none"> Ibutilide 1 mg IV TEE with successful cardioversion 	<ul style="list-style-type: none"> Recovered without sequela
Cardiogenic Shock	One day post-procedure patient became symptomatically hypotensive	<ul style="list-style-type: none"> Inotropes IABP 	<ul style="list-style-type: none"> Home inotropes Listed for Heart Transplant
Fever	Approximately 6 hours after the implant procedure, the patient developed a fever of 100.6, with a temperature max of 101.2.	<ul style="list-style-type: none"> Blood cultures negative No treatment rendered 	<ul style="list-style-type: none"> Fever resolved without intervention Recovered without sequela
Groin Hematoma	One day post-procedure, oozing was noted at the cath site. Physical inspection was negative for a hematoma however the cath site did have a steady ooze.	<ul style="list-style-type: none"> Right groin was injected with 3 cc lidocaine/epinephrine Pressure dressing and manual pressure was applied for 20 minutes. 	<ul style="list-style-type: none"> Recovered without sequela
Groin pain	Following the implant procedure, the patient complained of right groin pain.	<ul style="list-style-type: none"> Discharge postponed in order to observe patient for an additional day. 	<ul style="list-style-type: none"> Recovered without sequela
Hemoptysis	Patient developed mild hemoptysis during the procedure	<ul style="list-style-type: none"> Observed post procedure with no significant pulmonary abnormalities developing on chest x-ray 	<ul style="list-style-type: none"> Hemoptysis resolved without intervention Recovered without sequela
Stopped Coumadin for implant	INR remained subtherapeutic after implant and re-initiation of Coumadin	<ul style="list-style-type: none"> Patient remained hospitalized until INR therapeutic due to history of mechanical valve 	<ul style="list-style-type: none"> Recovered without sequela

Combined DSRC and Procedure Related Adverse Events

- DSRC – 8
- Procedure related – 7
- Combined – 15 (no overlap)
- $15/550 = 2.7\%$

Supplementary Analyses Over Study Duration

- Subjects remained in their assigned group until the last subject completed 6 months of follow-up.
- Many subjects remained in the study beyond 6 months.
- Mean follow-up was 15.7 months (range 1 day to 31 months)
- Principal endpoints analyzed based on information from the entire study duration

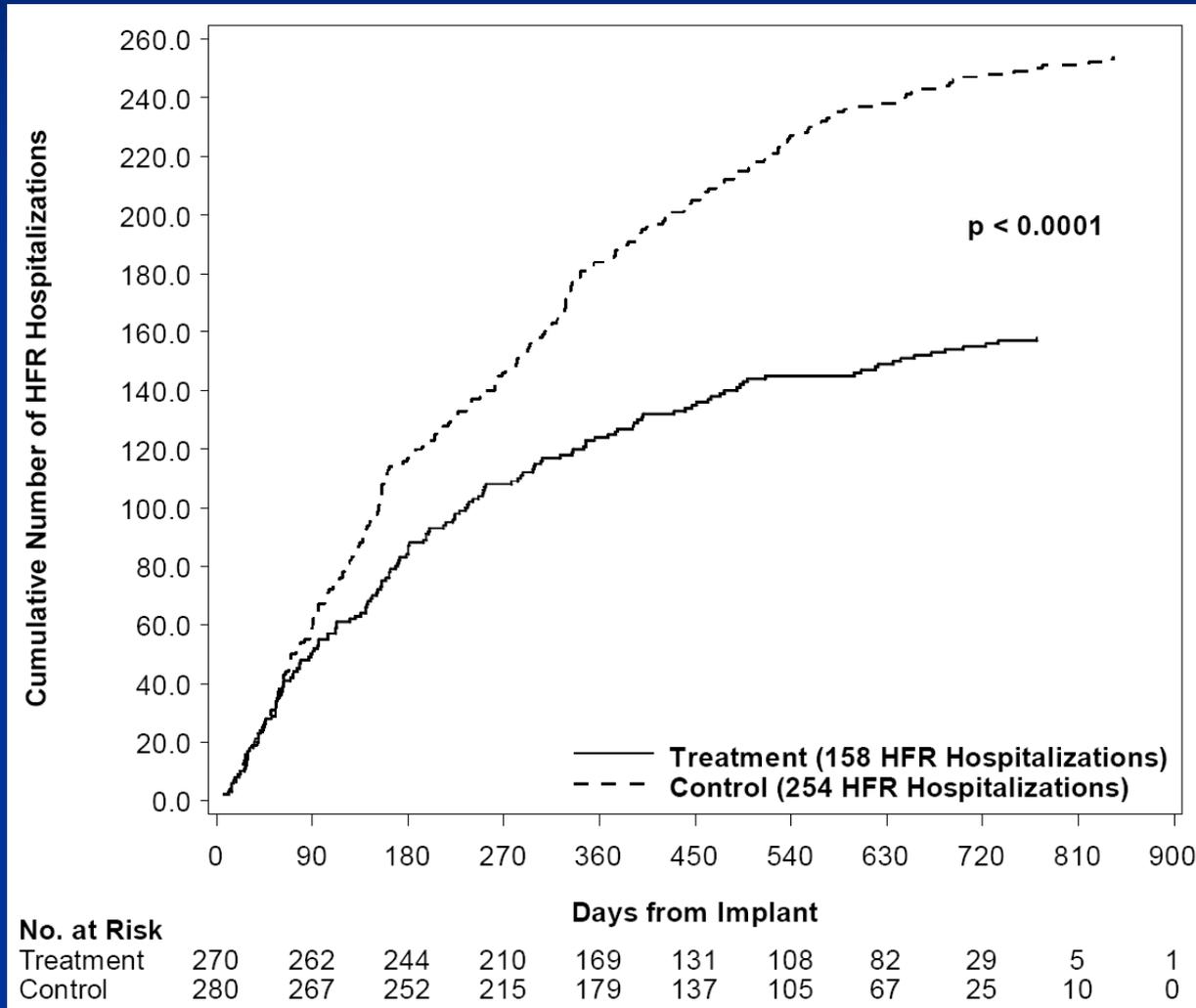
Principal Safety Endpoints Over Study Duration

- After 6 months,
 - all available subjects (n=498) were free of Device and System Related Complications (DSRCs); therefore, freedom from DSRC was 100%.
 - all available pressure sensors (n=498) were free of pressure sensor failure; therefore, freedom from pressure sensor failure was 100%.

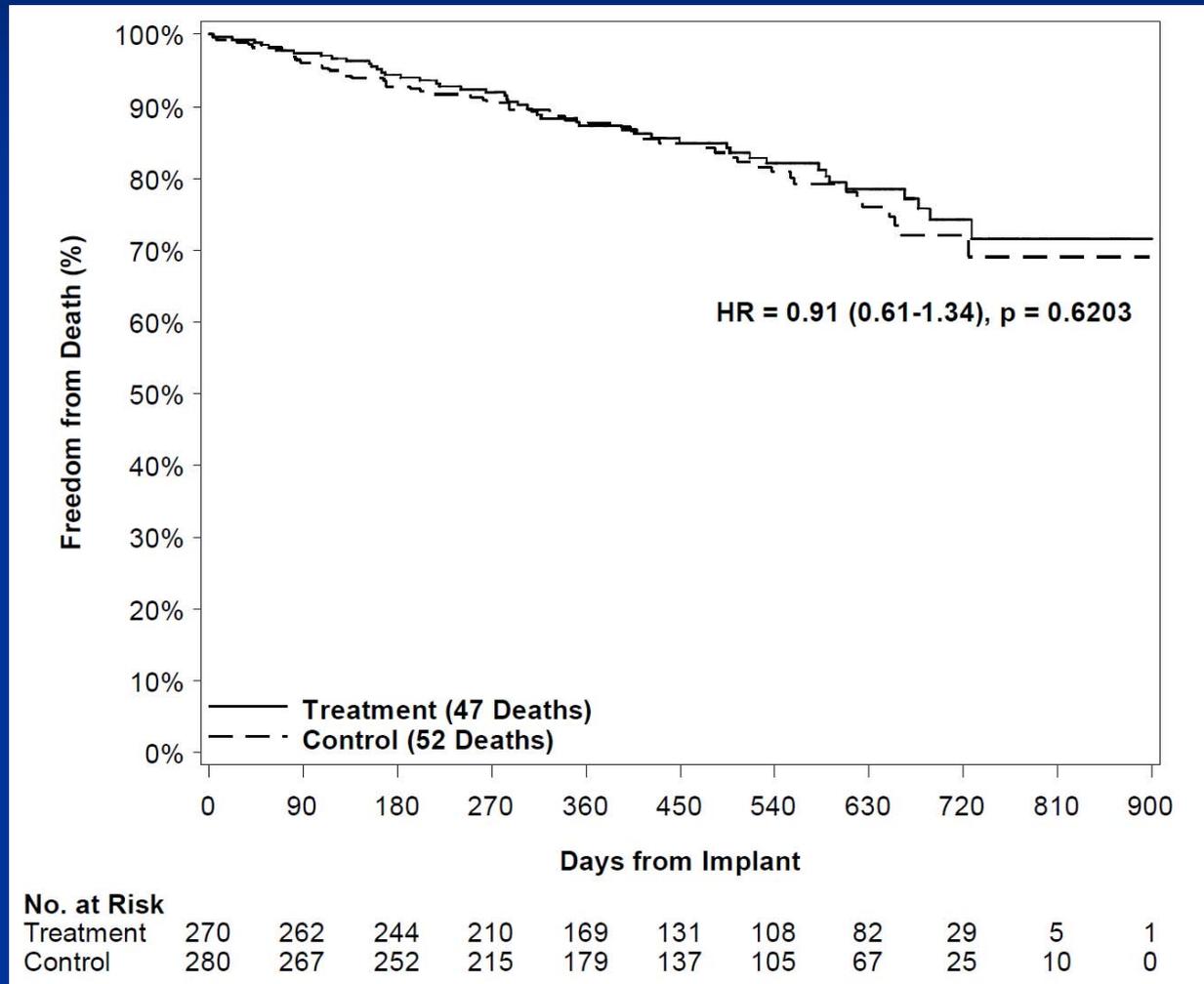
HFR Hospitalization Rate Over Study Duration

	Treatment (270)		Control (280)		
	# Hosp	Hosp Rate (events/pt-year)	# Hosp	Hosp Rate (events/pt-year)	p-value
Entire Blinded Randomized Period	158	0.46	254	0.73	<0.0001

Cumulative Heart Failure Related Hospitalizations over the Study duration



Kaplan-Meier patient survival plot over the study duration



Safety Summary Over 6 Months

- Both Primary safety endpoints were met.
- There was no substantial difference in 6 month survival.
- The 6 month Serious Adverse Event rate was ~50% in both groups and the combined procedure and 30 day adverse event rate was ~ 13%.
- Renal function did not appear to be substantially impacted by pressure-guided treatment.
- There was no clear evidence that the presence of the sensor contributed to pulmonary embolism.

Effectiveness Summary Over 6 Months

- The primary effectiveness endpoint (HFR hospitalization rate) was met from a statistical perspective
- Risk reduction is from 0.44 to 0.32 HFR hospitalization events/patient-6 months
- The Panelists will be asked to discuss the clinical significance of this finding
- Secondary endpoints for the proportion of subjects hospitalized for heart failure and for QOL were also met.
- Risk reduction in proportion of subjects hospitalized for HF is from 28.6% to 20.4% of patients with at least one HFR hospitalization. Difference in MLWHFQ score at 6 months was 5.4 points.
- The Panelists will be asked to discuss the clinical significance of these findings

The Most Common SAEs Prior to 6 Months

	Treatment (270)		Control (280)		Total (550)	
	Subjects	Events	Subjects	Events	Subjects	Events
CHF	59 (21.9%)	105	82 (29.3%)	130	141 (25.6%)	235
MI/ACS/Chest Pain	16 (5.9%)	21	19 (6.8%)	25	35 (6.4%)	46
Ventricular Arrhythmia	6 (2.2%)	6	11 (3.9%)	16	17 (3.1%)	22
Pulmonary Infections	9 (3.3%)	11	11 (3.9%)	12	20 (3.6%)	23
Renal Dysfunction/Failure	16 (5.9%)	16	10 (3.6%)	10	26 (4.7%)	26
Hypotension	8 (3.0)	11	7 (2.5%)	8	15 (2.7%)	19
Dehydration	5 (1.9%)	6	1 (0.4%)	1	6 (1.1%)	7

Serious Adverse Events After 6 Months

	Treatment (244)	Control (254)	Total (498)
Subjects	129 (52.9%)	137 (53.9%)	266 (53.4%)
Events	353	434	787

Pulmonary Embolism

- No pulmonary embolism events in 1st 6 months
- After 6 months, two (2) pulmonary embolism events were reported.
 - One subject had lower extremity thrombus as assessed by Doppler
 - One subject underwent a heart transplant with subsequent surgery to remove remnants of the ICD. The PE occurred 5 days after the ICD removal surgery.

Pulmonary Embolism (cont.)

- To further assess, FDA requested autopsies
- 5 autopsies obtained out of 99 pivotal trial deaths
- 1 autopsy from feasibility subject
- 5/6 revealed no evidence of PE
- 1 (pivotal study subject)
 - several chronic pulmonary emboli in the lung contralateral to sensor implant location
 - single embolus/infarction on side of implant

Proportion of Subjects Hospitalized for Heart Failure

	Treatment (270)	Control (280)	Total (550)	p-value
Heart Failure Hospitalizations				
Hospitalized	55 (20.4%)	80 (28.6%)	135 (24.5%)	
Not Hospitalized	215 (79.6%)	200 (71.4%)	416 (75.5%)	
Fisher's exact test				0.0292

Secondary Effectiveness Question

- This secondary effectiveness endpoint was met from statistical perspective
- Risk reduction is from 28.6% to 20.4% of patients with at least one HFR hospitalization
- Absolute risk reduction is 8.2%

- The Panelists will be asked to discuss the clinical significance of this finding

Days Alive Outside of the Hospital

Endpoint	Treatment Group	Control Group	Absolute Difference
Days Alive Outside of Hospital	174.4 ± 31.1	172.1 ± 37.8	2.3
# of days Hospitalized	2.2	3.8	1.6

The Panelists will be asked to discuss the clinical significance of the Days Alive Outside of the Hospital result and the absolute risk reduction that was observed.

Quality of Life

	Treatment (270)	Control (280)	Total (550)	p-value
6 Month Total Score				
Mean ± StdDev (N)	45.2 ± 26.4 (229)	50.6 ± 24.8 (236)	48 ± 25.7 (465)	0.0236
Median	45.0	52.0	49.0	

Quality of Life (*post hoc*)

	Treatment (270)	Control (280)	Total (550)	p-value
6 Month Change from Baseline				
Mean ± StdDev (N)	-10.6 ± 24.9 (229)	-7.4 ± 24.9 (236)	-8.9 ± 25.0 (465)	0.0373
Median	-7.0	-5.6	-7.0	

Secondary Effectiveness Question

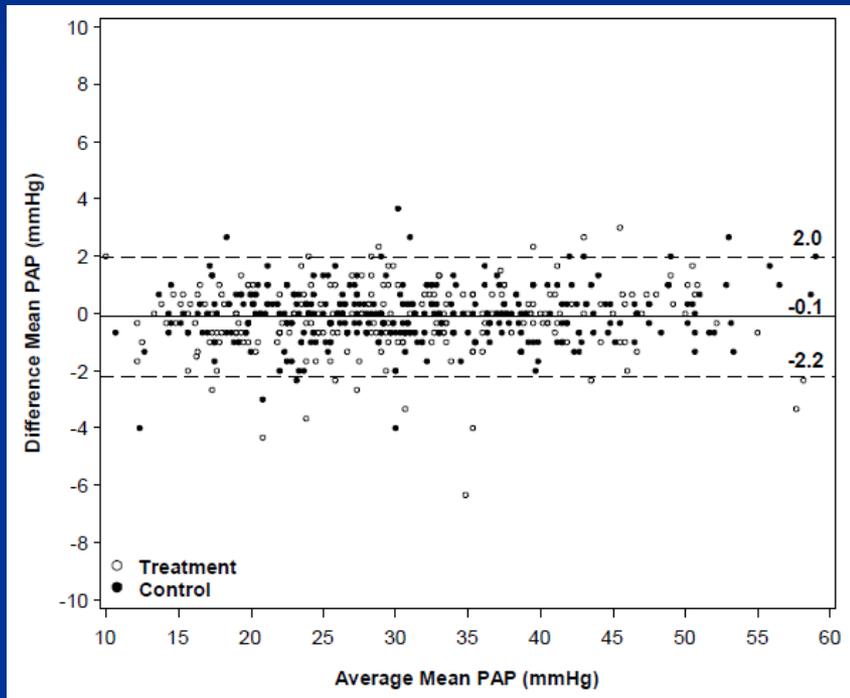
- The Quality of Life secondary effectiveness endpoint was met from statistical perspective
- Difference in MLWHFQ score at 6 months was 5.4 points
- The *post hoc* Quality of Life analysis indicates an improvement from baseline to 6 months for both groups, with a net change favoring Treatment over Control of 3.2 points.
- The Panelists will be asked to discuss the clinical significance of these results

Sensor Performance Analysis

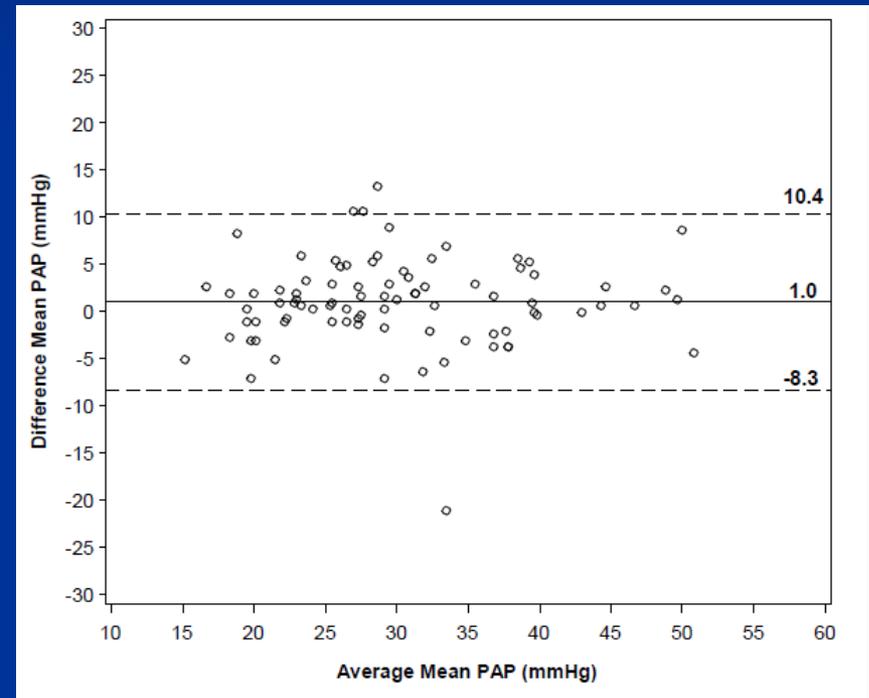
- During follow-up, repeat right heart catheterization (RHC) was not required
- 43 patients underwent 85 physician-initiated RHC procedures

Sensor Performance Analysis – Mean PA Pressures

Implant Measurement Comparisons

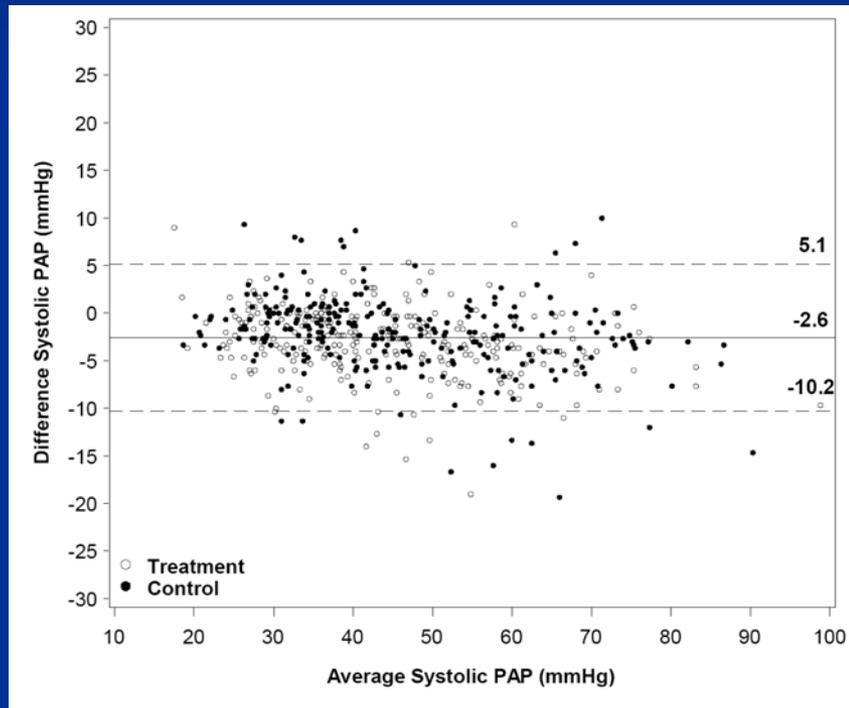


Follow-up Measurement Comparisons

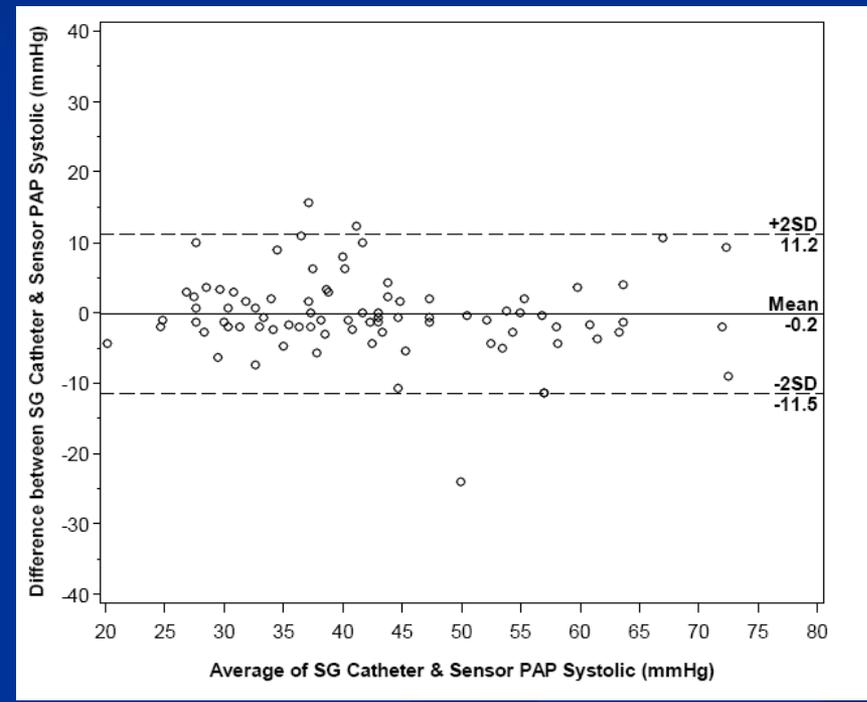


Sensor Performance PA Systolic

Implant Measurement Comparisons

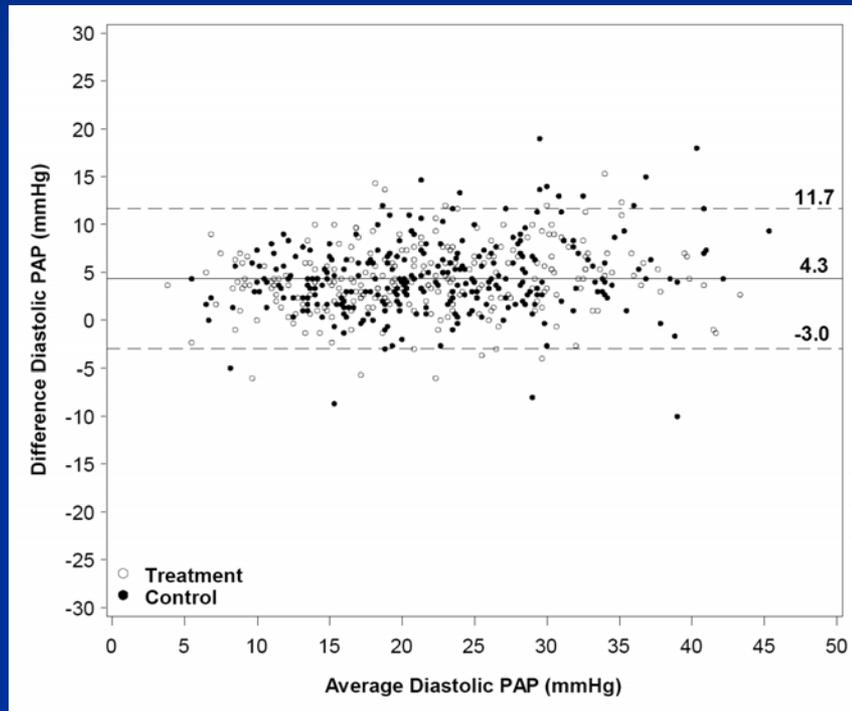


Follow-up Measurement Comparisons

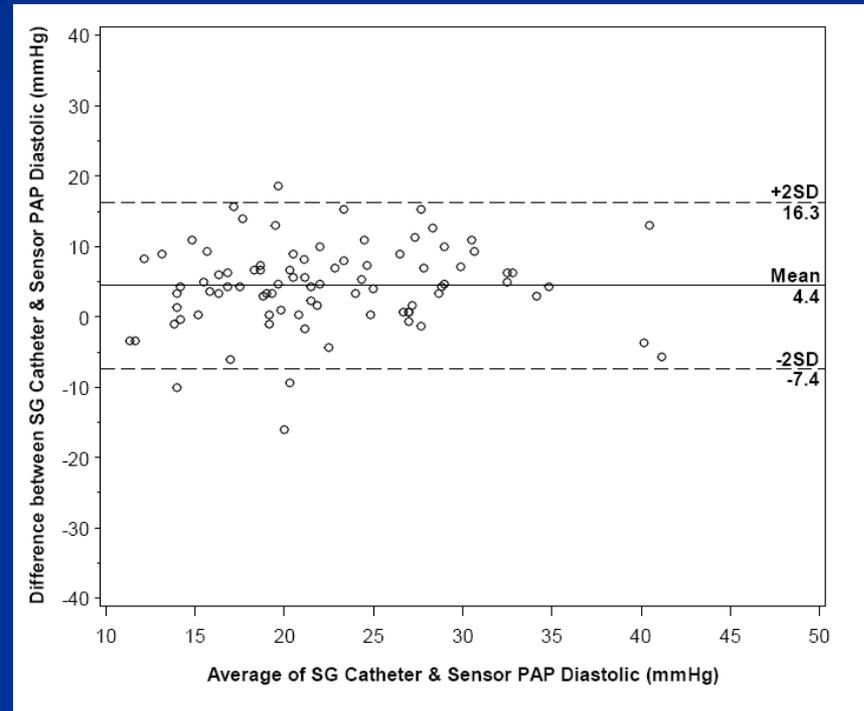


Sensor Performance PA Diastolic

Implant Measurement Comparisons



Follow-up Measurement Comparisons



Potential Bias Summary

- FDA is concerned that the management recommendations for individual study subjects in the Treatment arm only may bias the results of the trial.
- The Panelists will be asked to discuss this concern.

Treatment Recommendation Accepted #1

- On 2-10-2009, a CardioMEMS nurse wrote “1. *PCWP 36 with PAM 42 at implant- consider increasing Lasix mg dose or frequency.*” Several other recommendations were also made.
- Later that day, the site investigator wrote “*Great. I would like to see these regularly. Go ahead and have pt take extra 40mg of lasix daily at 2 pm for 5 days*”

Treatment Recommendation Accepted #2

- A CardioMEMS nurse wrote “[specific subject] responded nicely to the increase in lasix for 5 days however her PA Mean remains elevated. Are there any plans to continue her diuretic at a higher dose?”
- The site investigator responded “yes maintain higher dose Lasix and recheck chem 7 in a week”

Treatment Recommendation

Accepted #3

- On 5-28-2009, a CardioMEMS nurse *“I wanted to alert you to the spike in PA pressures for patient 03-011 SMT. I understand that she could not tolerate the Isordil because of headaches and only took it from April 1 - 16. My last conversation with Brittainy about this patient was that she was coming in for a visit around the middle of May and the plan was to assess her labs before making any additional changes in her medications and I believe you increased her Coreg to 12.5 mg bid at that time. Our records show the patient is on Lisinopril 40 mg q day, Hydralazine 25 mg tid, Coreg 12.5 mg bid, Aldactone 12.5 mg q day, and Lasix 40 mg q day”* and then wrote *“Do you think she could benefit from an increase dose of her Lasix or the addition of a prn dose of Metolazone?”*
- The site investigator responded an hour later *“check to see if anything new happened to explain increase. Did wt go up? Also give extra 40mg dose Lasix for 3 days then reassess. no metalazone”*

Treatment Recommendation

Accepted #4

- On 8-21-2009, a CardioMEMS nurse wrote “*I wanted to alert you to [specific subject]'s increase in pressures over the past week with a mean of 42 today. She responded nicely to extra lasix back in May. Would you consider this again?*”
- Four minutes later, the site investigator responded “*agree give extra dose for 3 days and check if anything different in terms of diet activity etc*”

Automated Email Message

A reading for a patient, has exceeded the following 1 threshold:

- PA Diastolic Pressure should be above 2 mmHg exceeded by - 1.0mmHg

Please visit the Champion HF System for further information.

Link to patient: <http://testing.championhf.com/patients/1>

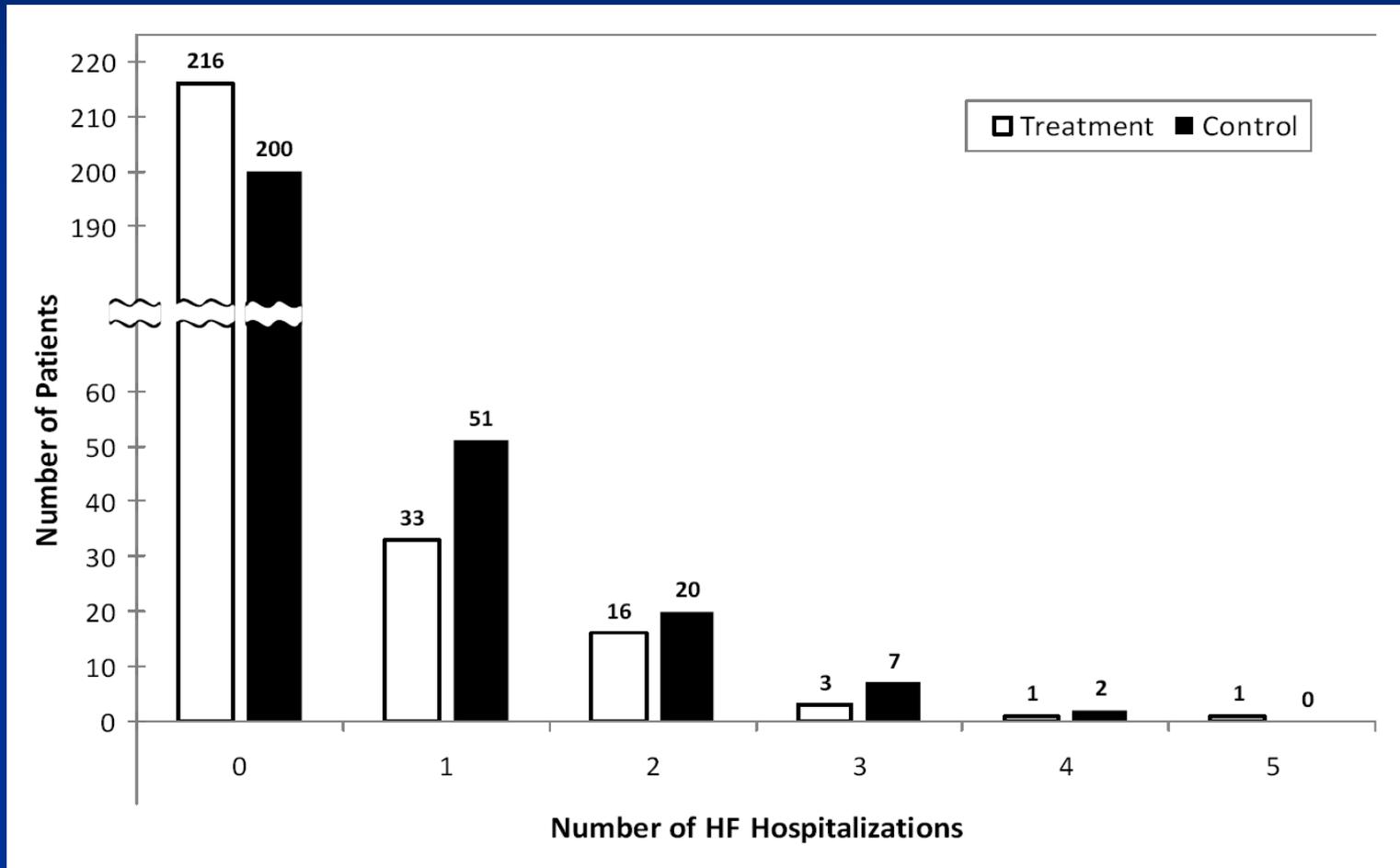
Please note, you can unsubscribe from email alerts for this patient by managing your subscriptions within the Champion HF System.

Thank you for using the CardioMEMS Champion HF System.

- CardioMEMS

* This email address is NOT monitored. Please do not reply.

Frequency of HFR Hospitalizations up to 6 Months



All-Cause Hospitalizations

	Treatment hospitalizations (6-month rate)	Control hospitalizations (6-month rate)
6 Months		
All Cause Hospitalizations	232 (0.86)	263 (0.96)
HFR Hospitalizations	84 (0.32)	120 (0.44)
Non-HFR Hospitalizations	148 (0.55)	143 (0.52)

CEC Adjudication of Hospitalizations to 6 Months

- See Sponsor Briefing document, Table 42, page 76 of 133

Hemoptysis

Number	SEVERITY	RELATED	DAYS AFTER IMPLANT
1	Mild	Unlikely	1
2	Mild	Unlikely	497
3	Moderate	Possibly	0
4	Mild	Not related	96
5	Mild	Not related	0
6	Severe	Not related	5
7	Severe	Possibly	0
8	Moderate	Not related	534

Compliance with Taking Home PA Pressure Readings

	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value[1]
Daily Readings (%)				
Median	89.4	85.7	88.0	0.1588
Mean±StdDev (N)	81.0±21.5 (270)	73.1±28.2 (277)	77.0±25.4 (547)	
(Min, Max)	(5.9, 100.0)	(2.2, 100.0)	(2.2, 100.0)	
[1]P-value testing the equality of distributions of daily readings between Treatment vs. Control using the Kuiper test				

Patient Study Visit Compliance

Protocol Deviations

Deviation Type	TREATMENT N=270	CONTROL N=280
Visit procedure not obtained per protocol	66	70
Visit was outside of window	49	76
Missed Visit	20	28
Subject did not meet Inclusion Criteria	5	0
INR >1.5 or not done at baseline	9	7
Post procedure medication	5	5
SAE not reported within 24 hours	0	4
Randomized after discharge	1	2
Device Implant Procedure	0	2
Subject Unblinded	0	3
Total	155	197

Blinding Analysis

Accuracy of Patient's Perception of Randomized Group	All Patients (261)	p-value [1]	Actual Randomized Group		p-value [2]
			Treatment (138)	Control (123)	
Correct, N (%) [95% Confidence Interval]	38 (14.6%) [10.3%, 18.8%]	<0.0001	24 (17.4%)	14 (11.4%)	0.2184
Incorrect/Does not know, N (%)	223 (85.4%)		114 (82.6%)	109 (88.6%)	
Incorrect	8 (3.1%)		4 (2.9%)	4 (3.3%)	
Does not know	215 (82.4%)		110 (79.7%)	115 (93.5%)	

Potential Admission Decision Bias

	6 Month		p-value
	Treatment Hospitalizations	Control Hospitalizations	
Admitted from Study Visit	8	9	0.5485
Admitted through ER	59	91	<0.0001
Elective Admission or Admission from Clinic	17	20	0.3125
Total	84	120	0.0002

HFR Hospitalization Rate at 6 Months by LVEF

	TREATMENT (270)			CONTROL (280)			ALL PATIENTS (550)
	# Pts. (n)	# Hosp. (n)	Hosp. Rate (events/patient-year)	# Pts. (n)	# Hosp. (n)	Hosp. Rate (events/patient-year)	NBR p-value[1]
EF < 40%	208	73	0.36	222	101	0.47	0.0085
EF ≥ 40%	62	11	0.18	57	19	0.33	<0.0001
[1] P-value from the negative binomial regression (NBR) model.							

Feasibility Studies

Study #	Patients Enrolled (#)	Study Sites (#)	Country	Study Start – Completion	Implant Technical Success Rate (%)
CM-05-04	28	3	Chile and Brazil	12/05 – 4/07	89
CM-06-05	10	1	Germany	10/06 – 9/08	90
CM-06-03	17	5	United States	12/06 – 8/07	100

Feasibility PA Pressure Correlation with SG Catheter

Pulmonary Artery Pressures by Sensor and SG at 60 Day Follow-Up

Feasibility PA Pressure Correlation with SG Catheter

Pulmonary Artery **Mean** Pressure by Sensor and Swan-Ganz (SG) Catheter for CM-05-04

Feasibility PA Pressure Correlation with SG Catheter

Pulmonary Artery **Systolic** Pressure by Sensor and Swan-Ganz (SG) Catheter for CM-05-04

Follow-Up Timepoint	Comparison Sample Size (n)	Sensor (mm Hg)		SG Catheter (mm Hg)		Sensor – SG Difference (mm Hg)		Pearson Correlation Coefficient (r)
		Mean	St. Dev.	Mean	St. Dev.	Mean	St. Dev.	
6 month	8	57	18	55	21	1	5	0.98
Year 1	13	48	18	52	19	-5	8	0.91
Year 2	9	59	23	63	26	-5	9	0.94

Feasibility PA Pressure Correlation with SG Catheter

Pulmonary Artery **Diastolic** Pressure by Sensor and Swan-Ganz (SG) Catheter for CM-05-04

CM-05-04

- 28 subjects enrolled
- 6 deaths
 - None considered device related
- 16 subjects experienced 75 adverse events
 - Most common were HF and related Sx's (SOB, edema, weight gain, etc.)
 - 2 AEs considered device related
 - Puncture site hematoma
 - “complication of device insertion”

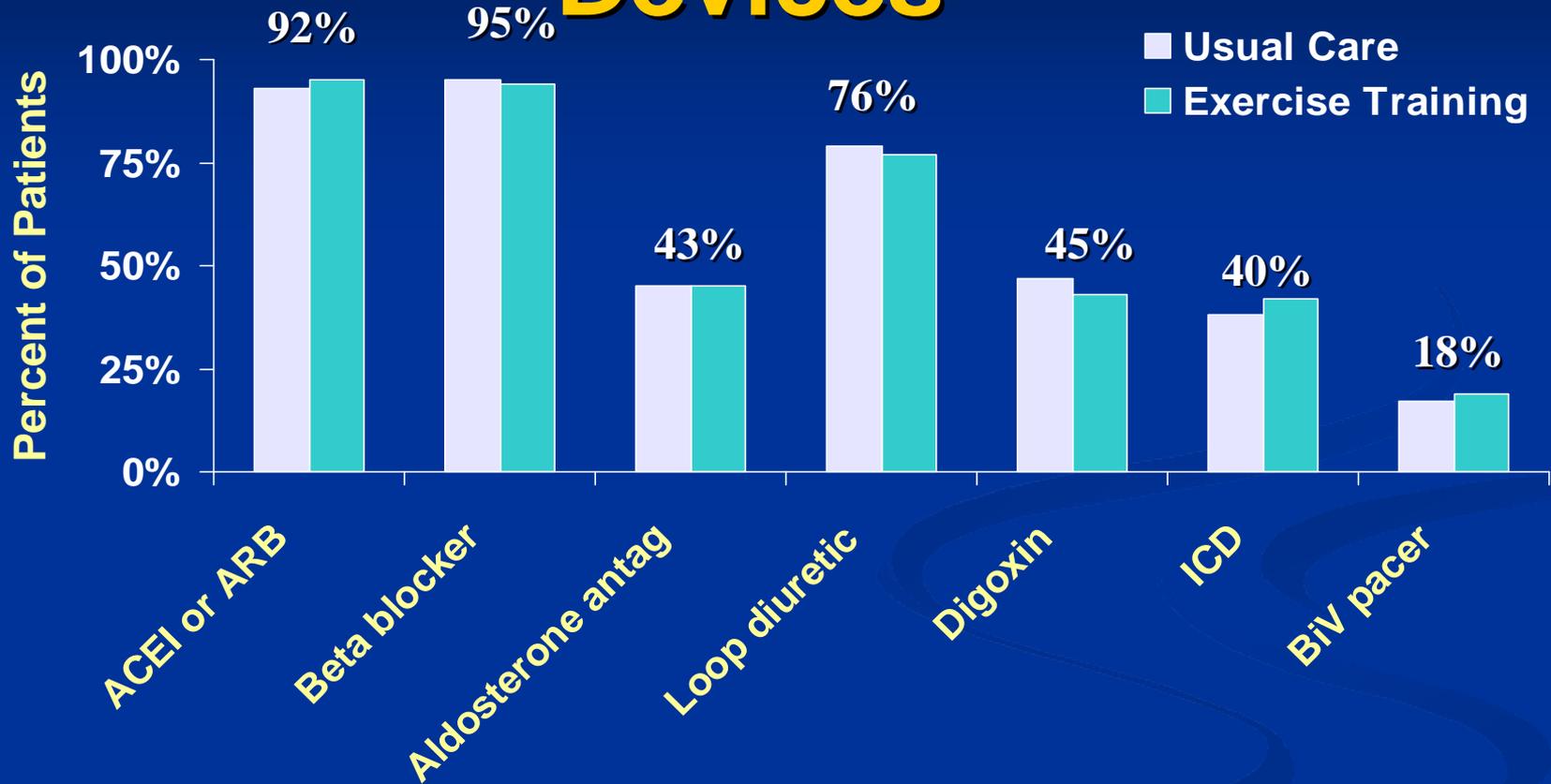
Medication Changes up to 6 Months by Reason for Change

Dr. Piña's Backup slides

Medical Therapy: Vasodilators at Baseline

	Baseline Treatment (n=270)	Baseline Control (n=280)	6 month Treatment (n=270)	6 month Control (n=280)
Hydralazine mg/day	140.1 ± 113.1 (n=34)	108.0 ± 63.98 (n=29)	173.4 ± 110.5 (n=34)	130.0 ± 91.9 (n=29)
Nitrates Mg/day	65.43 ± 36.92 (n=58)	51.67 ± 34.20 (n=51)	82.93 ± 58.07 (n=58)	55.39 ± 36.7 (n=51)

Baseline Medications and Devices



OPTIMIZE-HF

n=15,381

Table 3
Eligible patients treated with adjunctive therapy

Adjunctive Therapy (eligible patients)	Mean \pm SD for Sites	Median for Sites	25th, 75th Percentiles for Sites	10th, 90th Percentiles for Sites	Cumulative for Entire Cohort
Pneumococcal vaccination (n = 14,958)	1.0 \pm 3.30%	0.0%	0.0%, 0.0%	0.0%, 2.5%	172 (1.1%)
HYD/ISDN for Black patients (n = 1,369)	7.3 \pm 14.76%	0.0%	0.0%, 8.3%	0.0%, 25.0%	160 (11.7%)
Statin* (n = 11,784)	57.1 \pm 13.86%	56.9%	51.0%, 65.6%	40.0%, 73.3%	6,756 (57.3%)
Low-density lipoprotein <100 mg/dl (n = 11,784)	44.8 \pm 17.18%	45.3%	33.7%, 57.1%	21.4%, 67.5%	5,193 (44.1%)
Antiplatelet (n = 11,784)	64.6 \pm 12.91%	65.7%	60.4%, 72.0%	50.9%, 77.6%	7,721 (65.5%)
Smoking cessation (n = 1,788)	27.4 \pm 23.22%	25.0%	8.3%, 40.0%	0.0%, 61.1%	518 (29.0%)
Systolic blood pressure <140 mm Hg (n = 15,150)	82.0 \pm 6.00%	82.5%	78.7%, 86.0%	74.5%, 88.9%	12,399 (81.8%)
Systolic blood pressure <130 mm Hg (n = 15,150)	66.6 \pm 7.79	67.2%	61.5%, 71.2%	57.0%, 76.6%	10,085 (66.6%)

* Statin and antiplatelet therapy for CAD, cardiovascular disease, or peripheral vascular disease.

Yancy et al. Am J Cardiol 2010;105:255–260