CardioMEMS *Champion*™ Heart Failure Monitoring System

PMA P100045
IDE G060187

December 2011

Circulatory System
Devices Advisory Panel
Food and Drug Administration
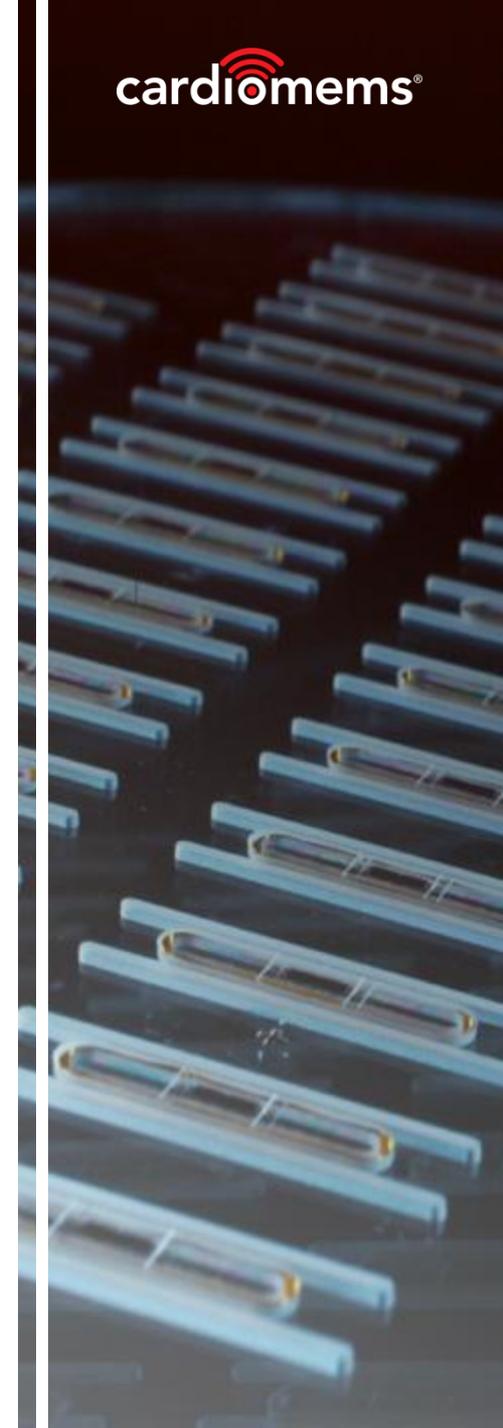
Introduction

Jay S. Yadav, MD, FACC
Founder and CEO, CardioMEMS, Inc.

Cardiologist, Piedmont Heart Institute

Chairman, Piedmont Innovation Center
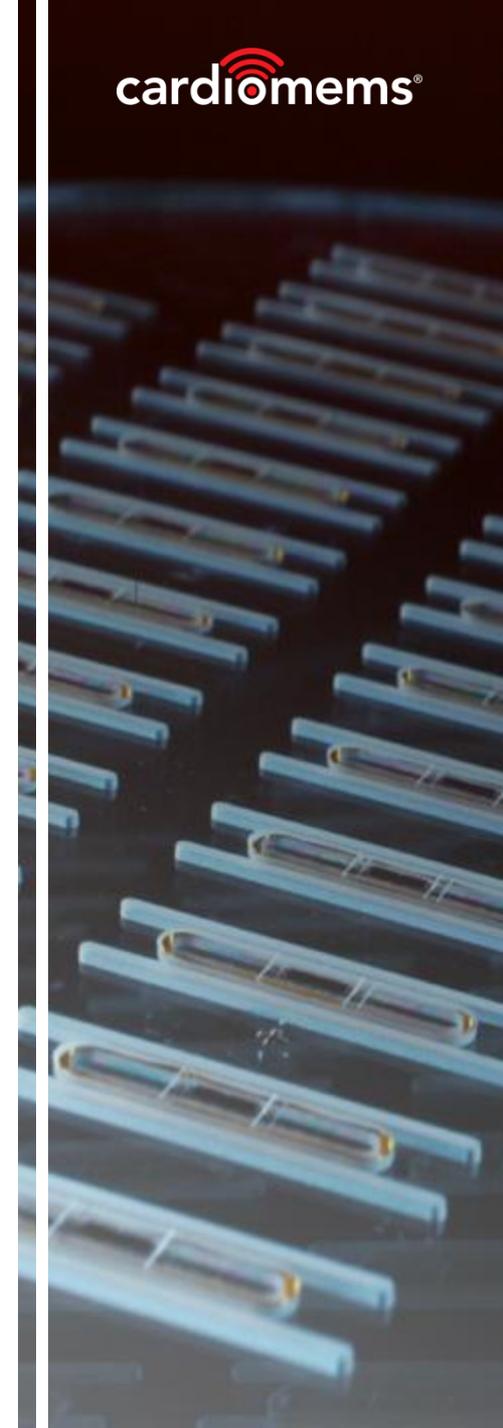
cardiomems®

CardioMEMS Objective

To demonstrate the safety

and efficacy of the CardioMEMS

Champion Heart Failure

Monitoring System

Overview: *Champion* HF Monitoring System

Background: Greater than 1 million HF hospitalizations per year at a $40B annual cost[1]

Premise: Ambulatory PA pressure measurements allow more effective HF management leading to fewer hospitalizations

Result: CHAMPION trial has demonstrated safety and efficacy
- ✓Met all Primary Safety and Efficacy Endpoints
- ✓Met all 4 Secondary Efficacy Endpoints

[1](2010). *American Heart Association Heart and Stroke Statistics.* Statistical Update.

CardioMEMS at a Glance

- Wireless Communication System for the Human Body

- MEMS- microelectromechanical systems

- Platform Technology

- Founded 2001, Atlanta,
  - Georgia Tech Incubator
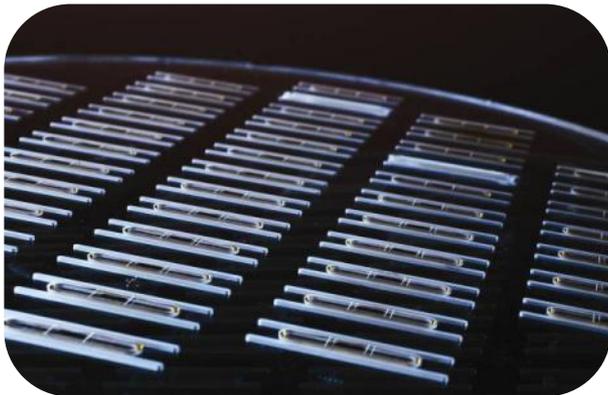
Sensor wafer

- FDA cleared in 2005, permanently implanted wireless sensor (AAA/TAA)
  - 8,000+ wireless sensors implanted
  - Sensor batch fabrication similar to semiconductor industry

- CE Mark for Class III heart failure

CardioMEMS *Champion* HF Monitoring System

Pressure Sensor on Catheter-based Delivery System

4.5cm

120cm
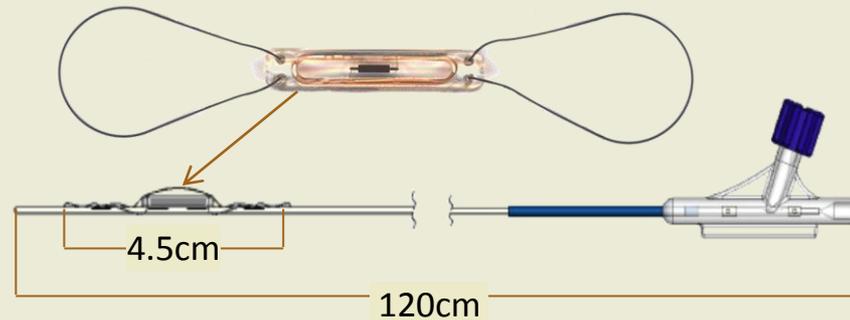
Home Electronics

PA Monitoring Database
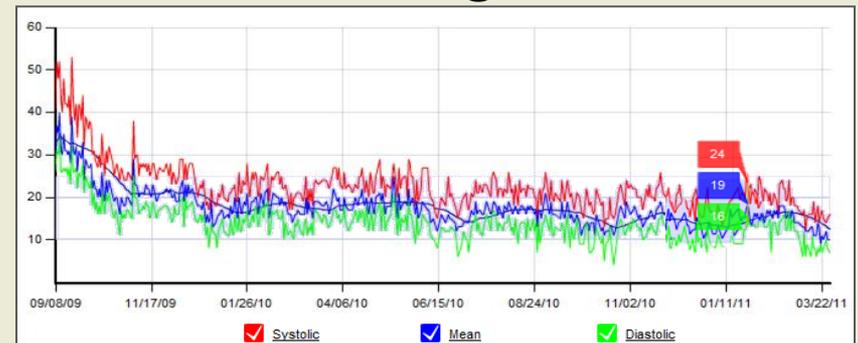
Proprietary database for secure storage of patient data

Sensor

Capacitance (C) and Resonant Frequency (f) vary with Pressure

Antenna

Z

Inductive Coupling

Z

Antenna Impedance

L C(P)

Sensor

$$f_0 = \frac{1}{2\pi \sqrt{L\ C_{(P)}}}$$

Nanometer deflections

1 μ gap variable capacitor

RF Coil

Pressure

Phase of Z

$f_{(P=max)}$ $f_{(P=0)}$
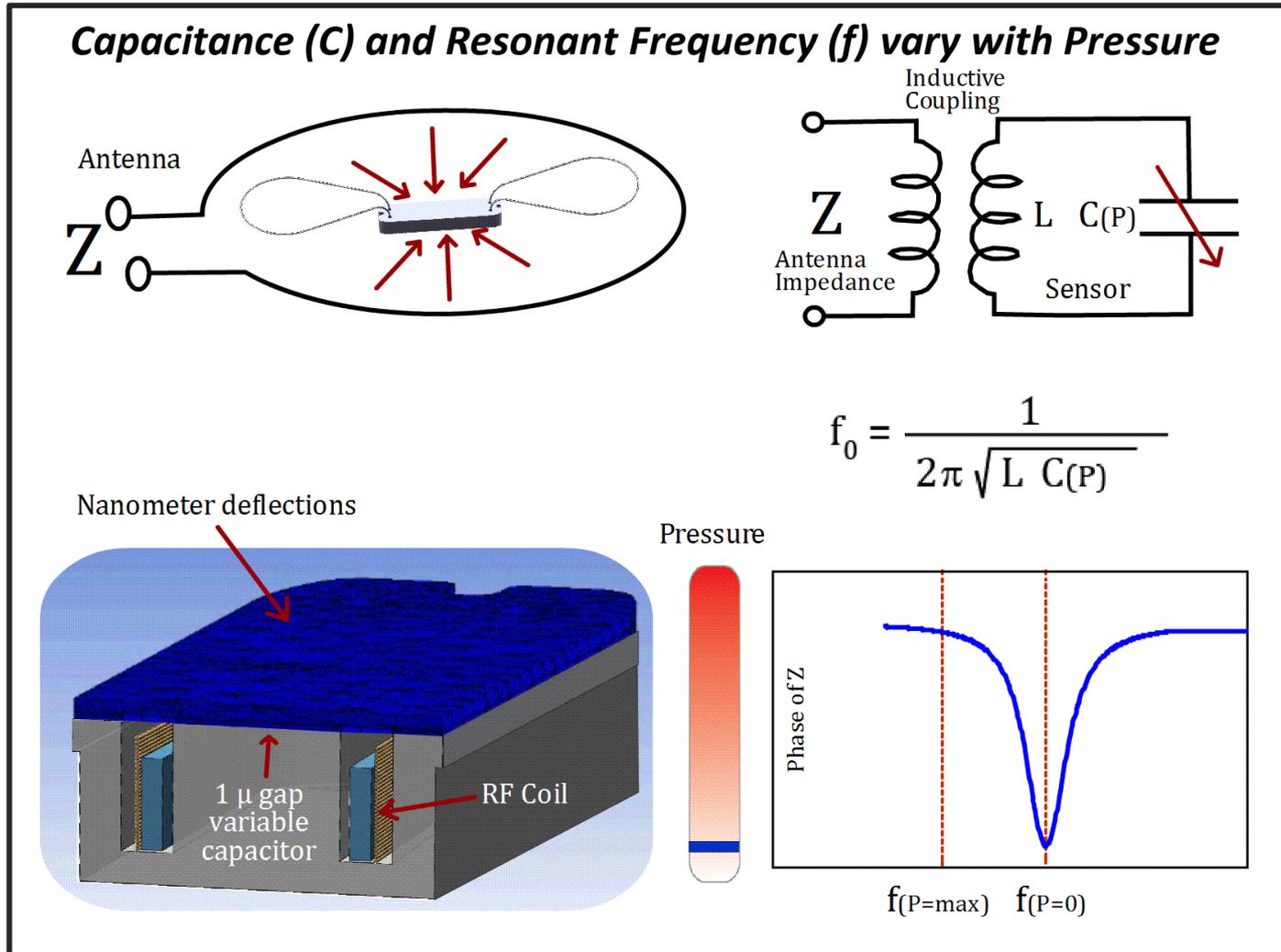
Georgia Institute of Technology, DARPA

Radio Frequency Power and Communication
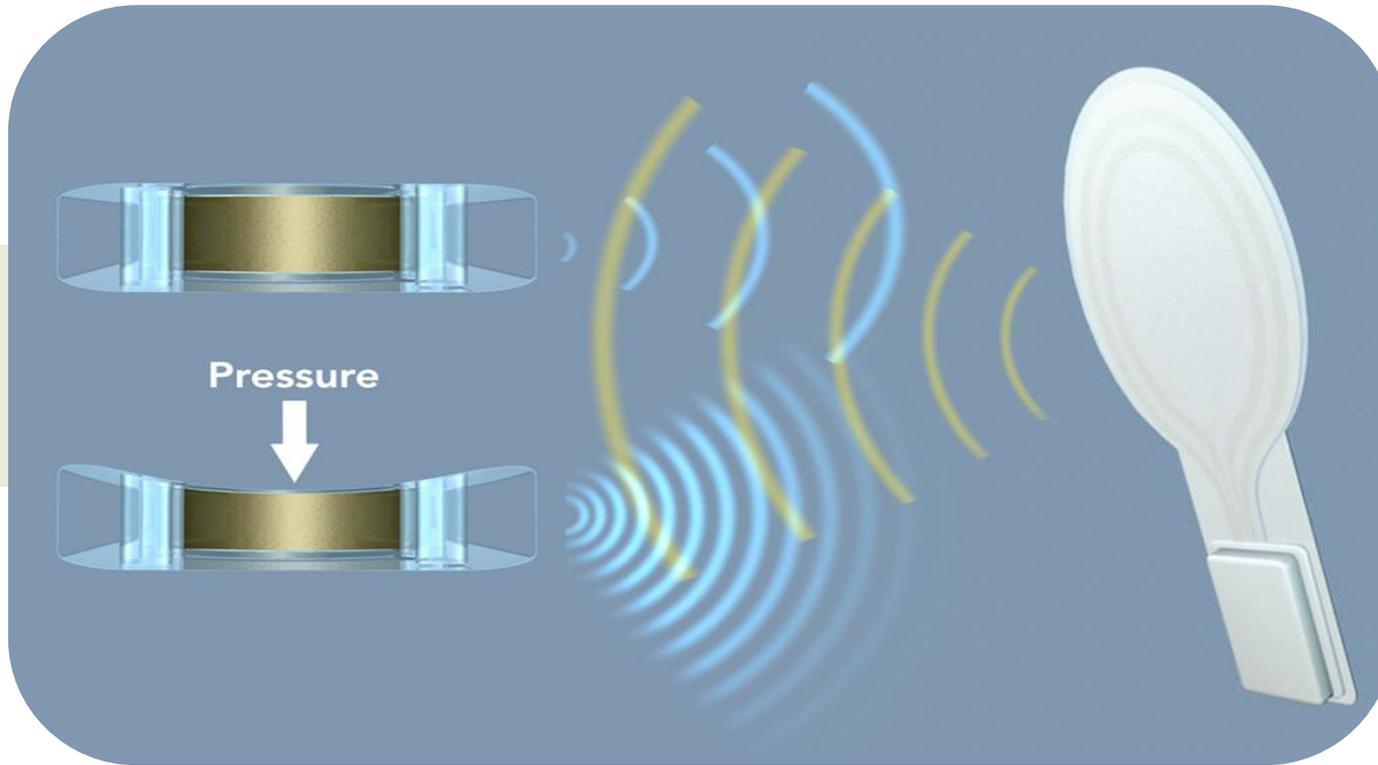
- Externally powered
- No battery

Pressure

CardioMEMS PA Waveform

- Smooth and undistorted 18 sec waveform
- Clear and pronounced dicrotic notch

MIT Media Lab

Design Features of the HF Pressure Sensor

Sensor:

- No Battery
- No Leads
- Small Size (3.5 x 2 x 15mm)

Sensor Wire Loops:

- Function: Maintain Sensor Position in Vessel
- Wire Material: Nitinol
- Wire Diameter: 0.006"
- Loop Diameter/Width: 10 mm

Pressure Sensitive Capacitor

Fused Silica Housing with Silicone Coating

Inductor Coil
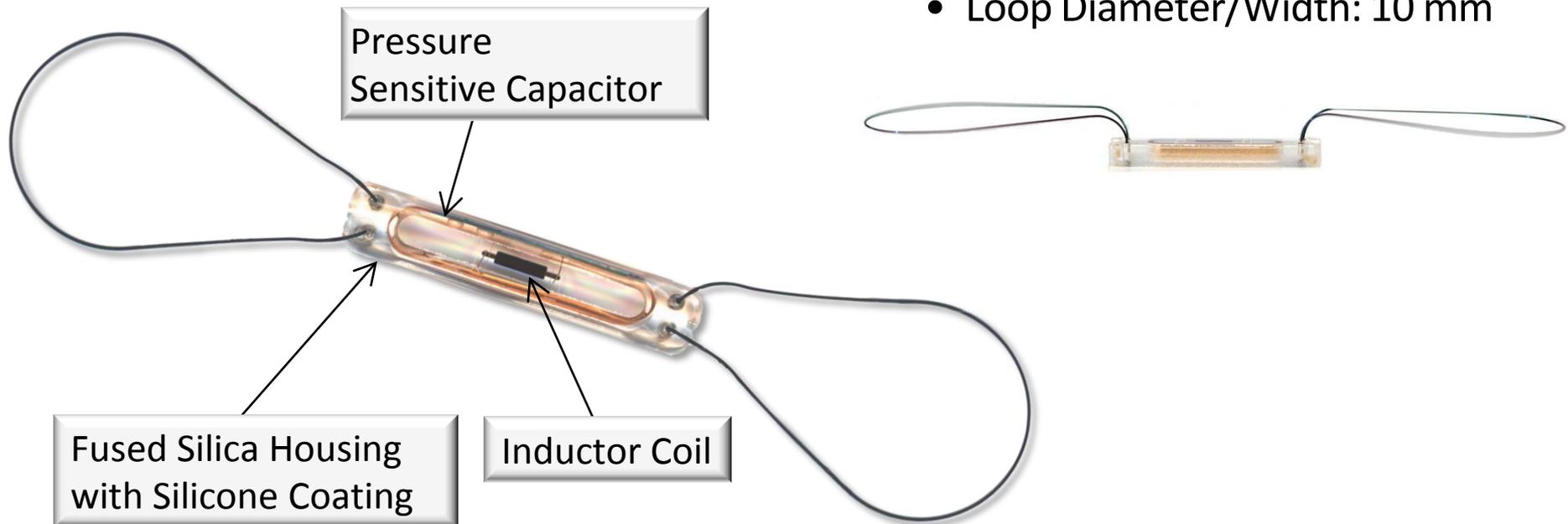
Design Features of the Sensor Delivery System

- Over-the-Wire Implant
- Tether release system
- Hydrophilic coating
- Radiopaque shaft
- Guidewire: 0.018"
- Introducer Sheath: 11Fr Terumo
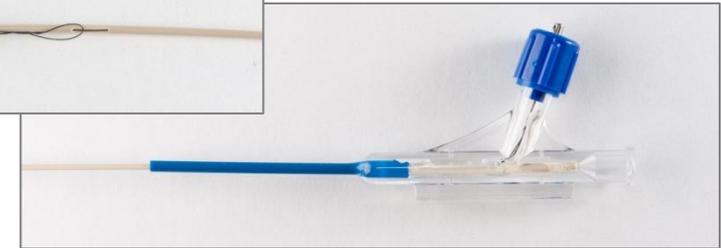
Sensor Implant
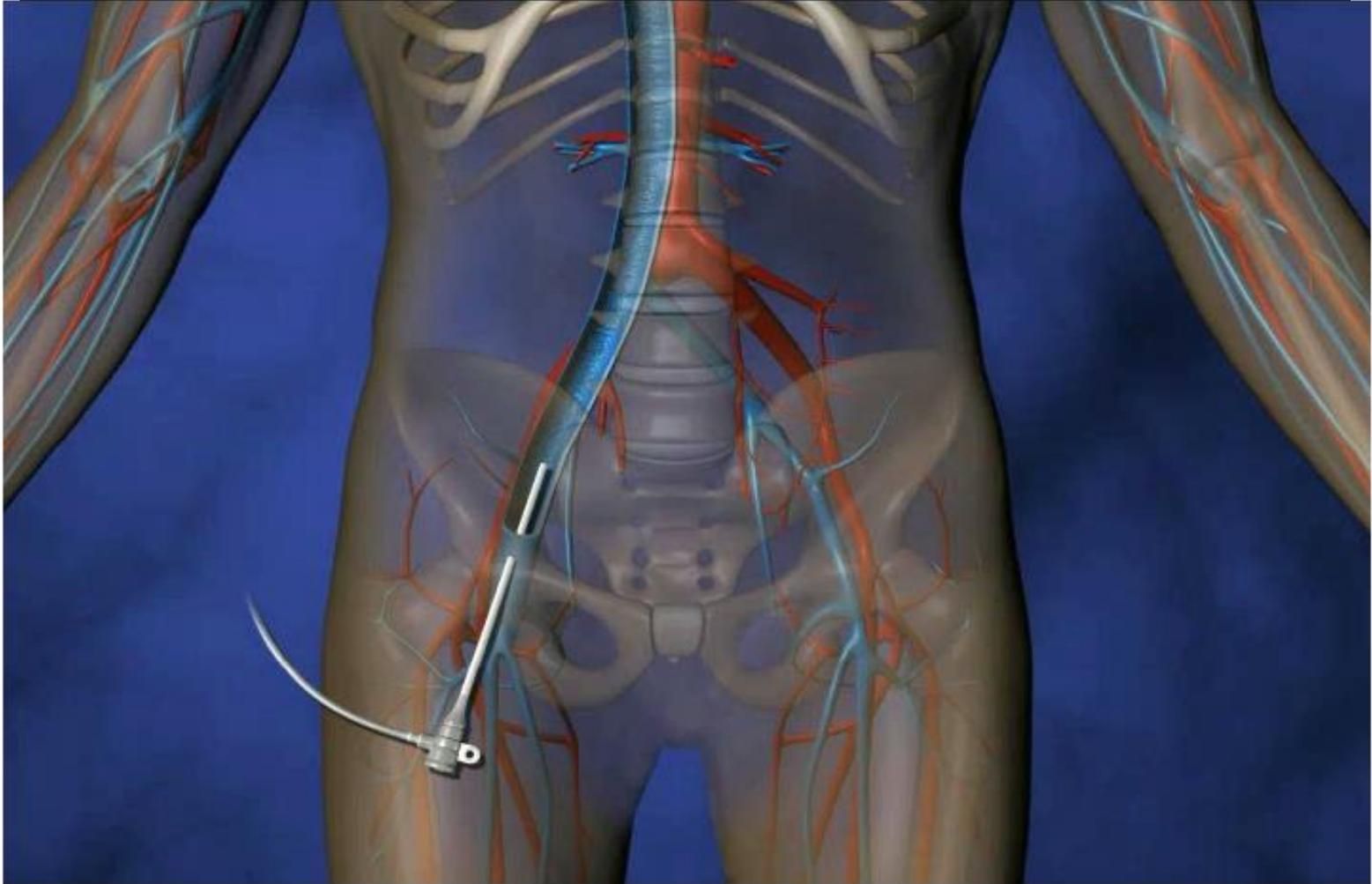
Intuitive Patient Management Database

Trend Data

- Easy-to-read
- Physician alerts
- Home transmission
- Secure, encrypted web-based access
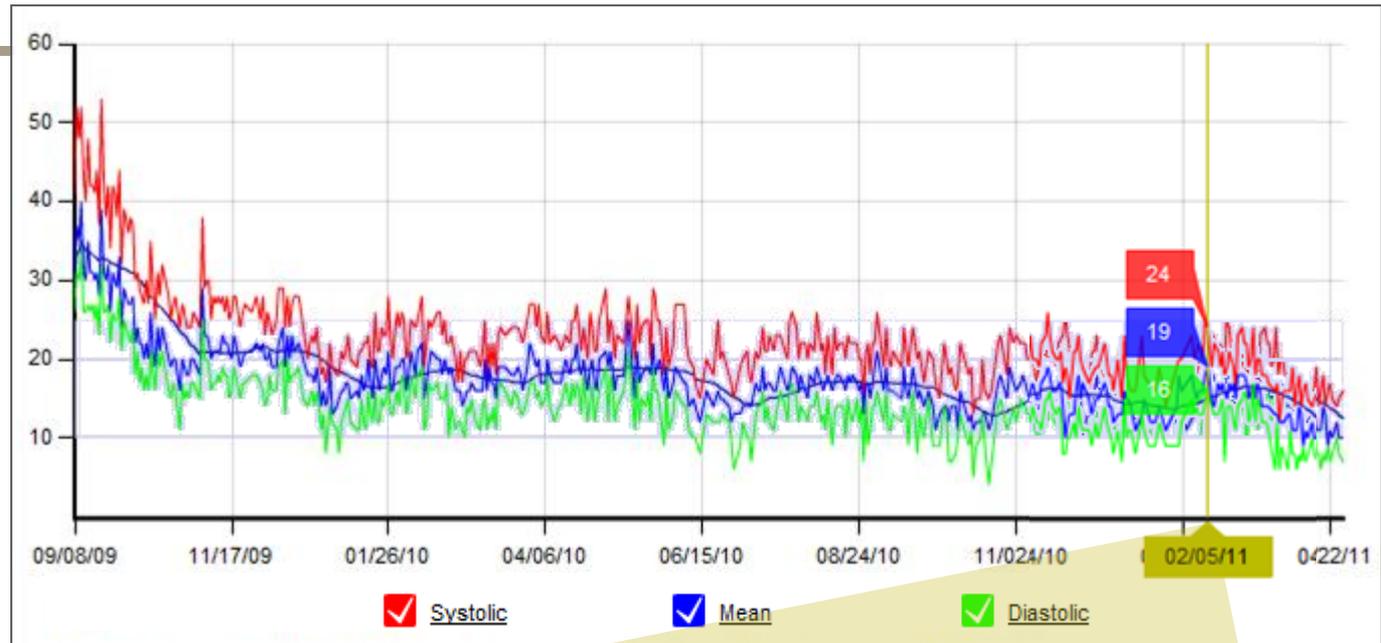
Discrete Data

Reading	
Systolic:	24
Mean:	19
Diastolic:	16
Heart Rate:	81
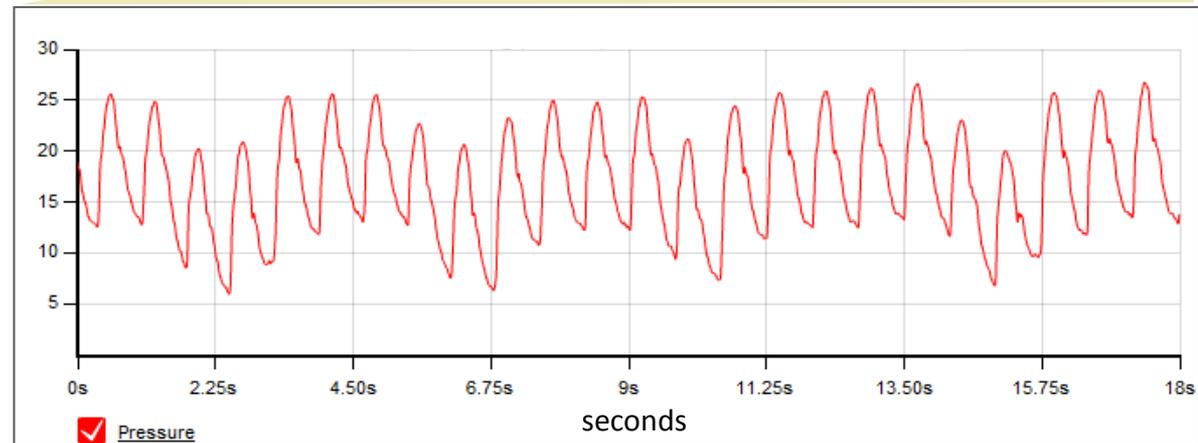
Expert Advisors

- Alan Miller, MD
  - Professor of Medicine, University of Florida, Jacksonville
  - Chairperson CEC
  - Disclosures: Compensation for CEC activities

- Robert Bourge, MD
  - Professor of Medicine, Radiology and Surgery; University of Alabama, Birmingham
  - Disclosures: Compensation as Clinical Investigator

- Stephan Ogenstad, PhD
  - Statistician, Statogen Consulting, LLC
  - Disclosures: Consulting fees from CardioMEMS

- Wayne Levy, MD, FACC
  - Medical Director, UW Regional Heart Center Clinic, Professor of Medicine/Division of Cardiology, University of Washington
  - Disclosures: Compensation for CEC activities

- Spencer Kubo, MD
  - Adjunct Professor, University of Minnesota
  - Disclosures: Consulting fees from CardioMEMS

Agenda

- ➢ Filling Pressures and Heart Failure Decompensation

  Dr. Lynne Warner-Stevenson
  Brigham and Women's Hospital

- ➢ CHAMPION Clinical Trial Design

  Dr. Philip Adamson
  Oklahoma Heart Hospital

- ➢ CHAMPION Clinical Trial Results

  Dr. William Abraham
  Ohio State University

- ➢ General Statistical Considerations

  Richard Holcomb, PhD
  Independent Statistician

- ➢ Medical Management

  Ty Cowart, MBA/MPA, JD, LLM
  CardioMEMS

- ➢ PAS, Training and Commercial Support

  Dr. Jay Yadav
  CardioMEMS

Filling Pressures as the Mechanism of Heart Failure Decompensation

Lynne W. Stevenson, MD, FACC

Director Cardiomyopathy and Heart Failure, Brigham and Women's Hospital, Boston, MA
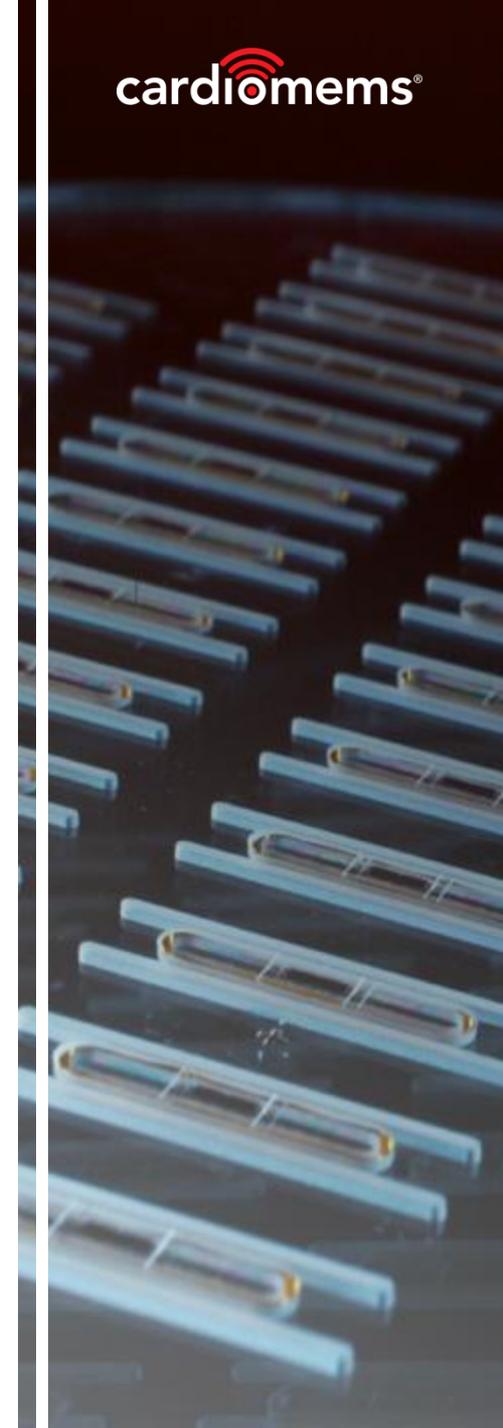
Cardiac Filling and Output In Dilated Heart Failure

Stroke Volume

Normal

Acute ischemia

Chronic dilated heart failure
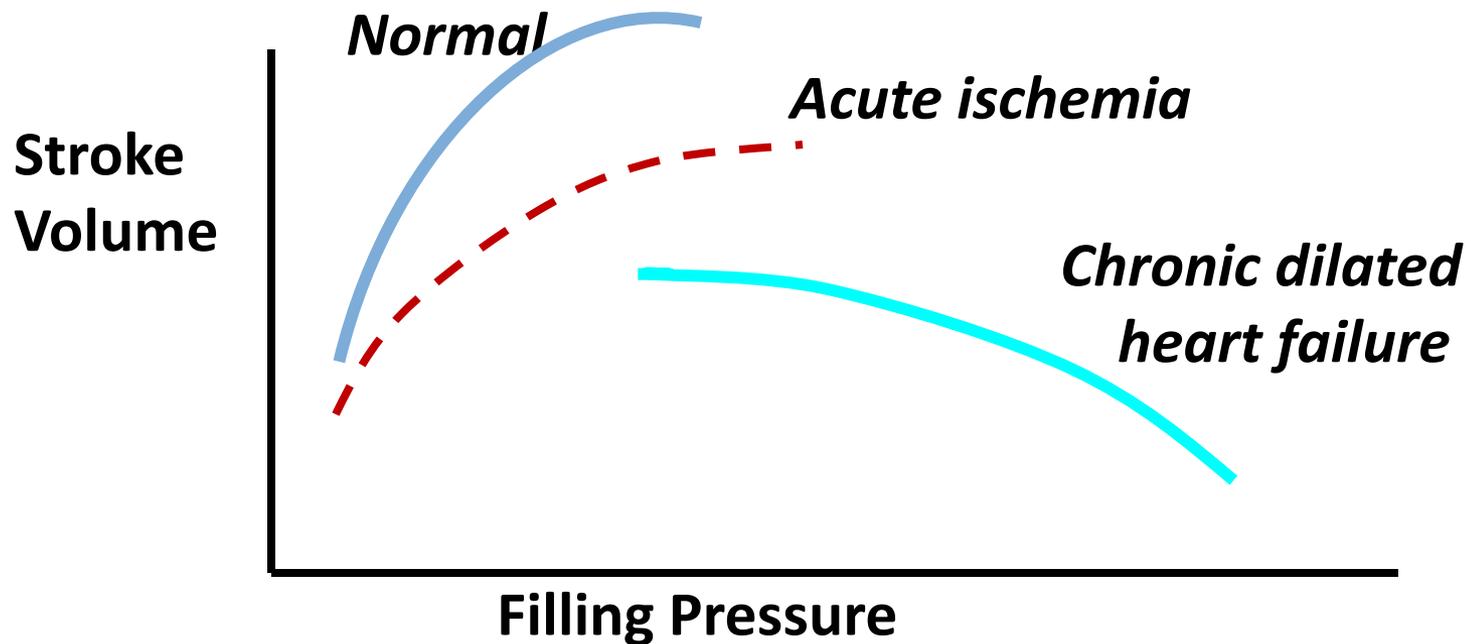
Filling Pressure

Starling
Russell and Rackley
Stevenson, Tillisch 1986

Most HF Prognostic Factors are Determined by Cardiac Filling Pressures

- Clinical:
  - Class IV status, orthopnea
  - S3, jugular venous distention
  - Increasing diuretic requirement

- Hormonal:
  - ANP, BNP, pro-BNP levels
  - ST2 levels

- Echocardiographic:
  - Mitral regurgitation, tricuspid regurgitation, mitral inflow, pulmonary venous flow patterns, mitral annular tissue Doppler

- Hemodynamic:
  - Cardiac filling pressures >> cardiac index

Discharge Filling Pressures Predict Outcomes

	Time to Death/ Rehospitalization
RAP	.22
PAD	.016
PCW	.0078
Cardiac Index	.88 Not Cardiac Index
Systolic BP	.0013

Worsening Outlook After Each Heart Failure Admission

Kaplan-Meier cumulative mortality curve for all-cause mortality after each subsequent hospitalization for HF.

Fourth Hosp

n = 1,123

n = 417

n = 3,358

1st Hosp

n = 14,374

Setoguchi et al

American Heart Journal
August 2007

2 Years

chf   ┼┼┼ 1st Admission   △△△ 2nd Admission   *-*-* 3rd Admission   ⊖⊖⊖ 4th Admission
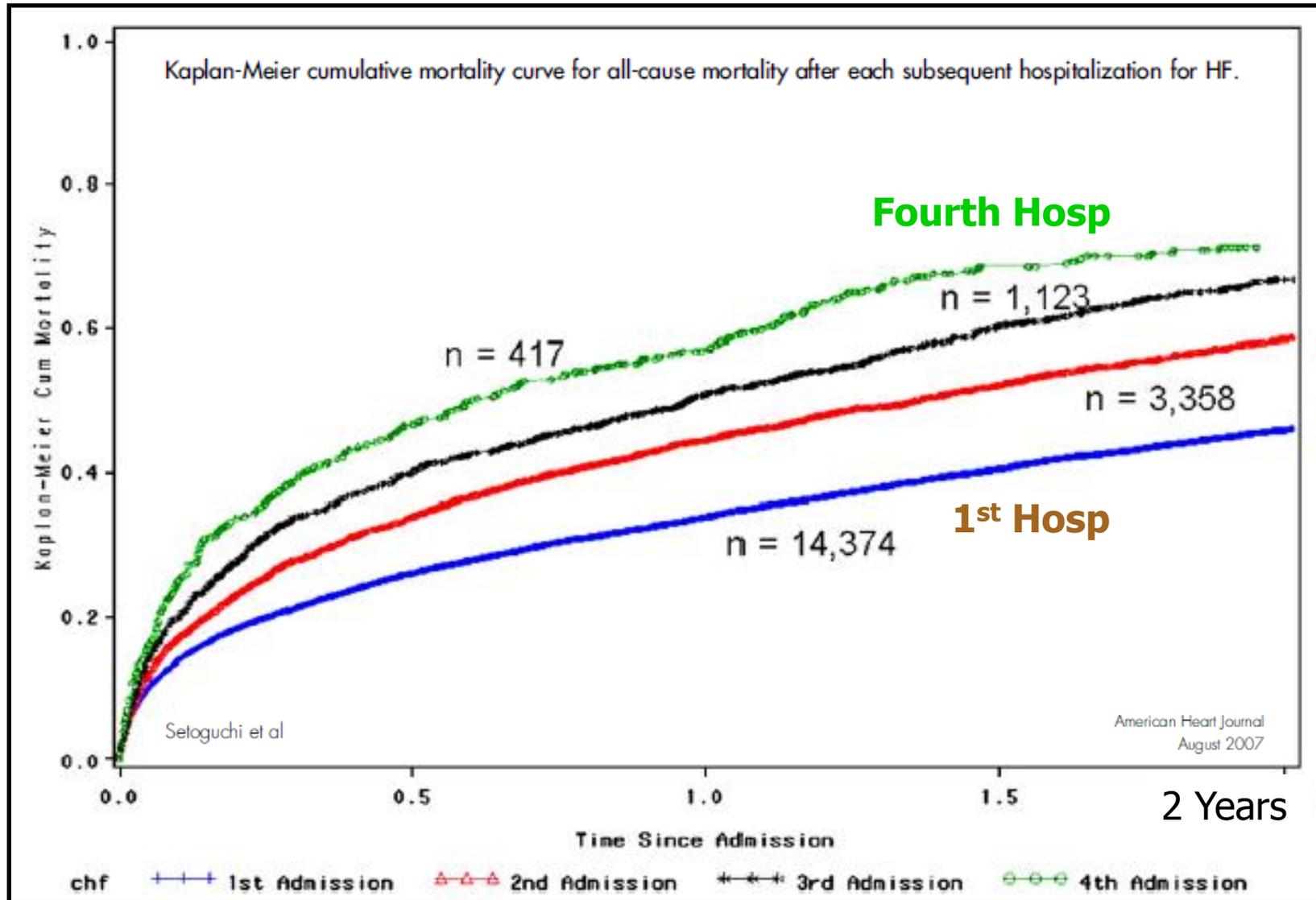
Most Days of Heart Failure Management Are Not Clinic Days

Legend:
- HF Clinic
- Device Clinic
- Home
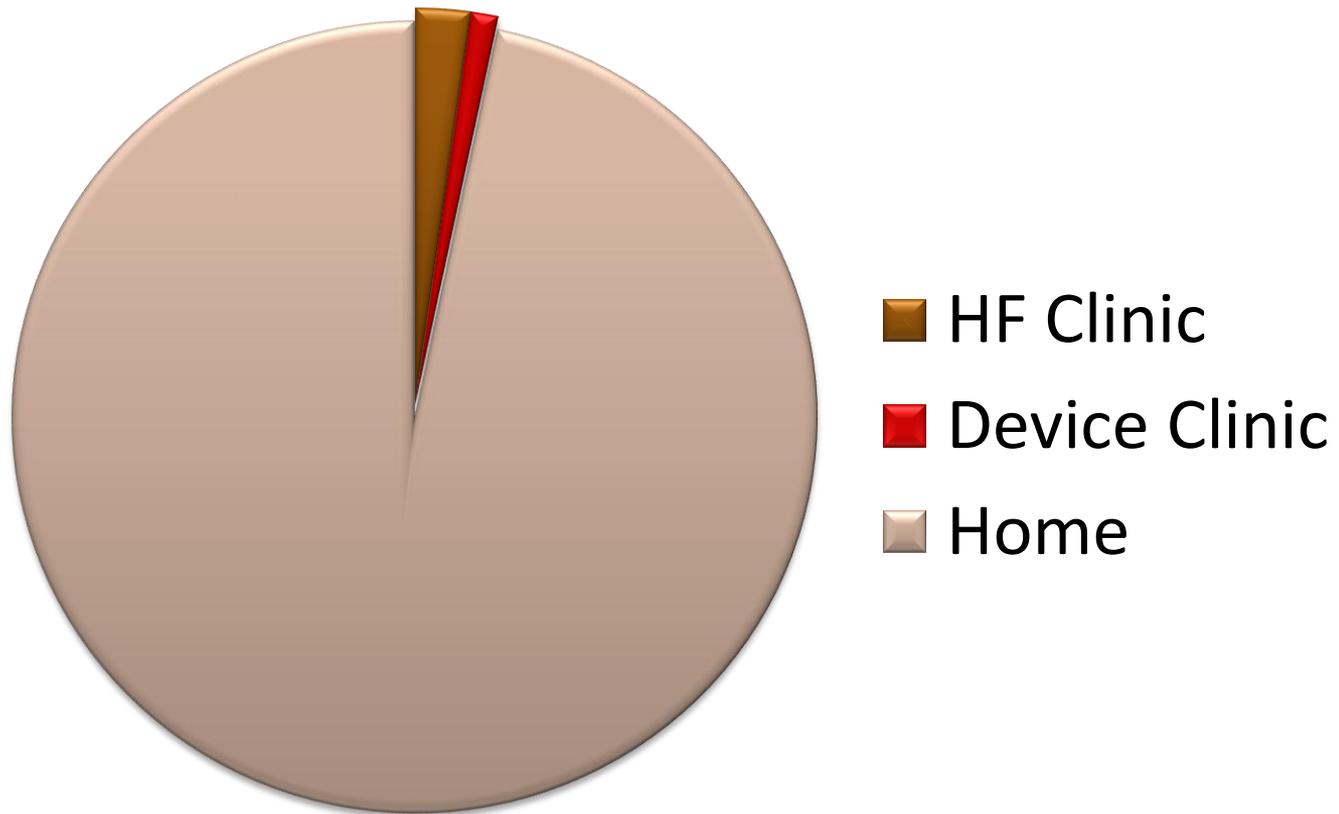
We Thought Weights Worked

- Because changes in weight often reflect changes in fluid during short intervals
  - Close relationship to net fluid loss in hospital
  - Rapid changes at home after intervention

- Because weight-guided management is so much better than nothing

- Because when they didn't work at home, we blamed the patients

Body Weight and RV Diastolic Pressure Before Hospitalization

Body Weight
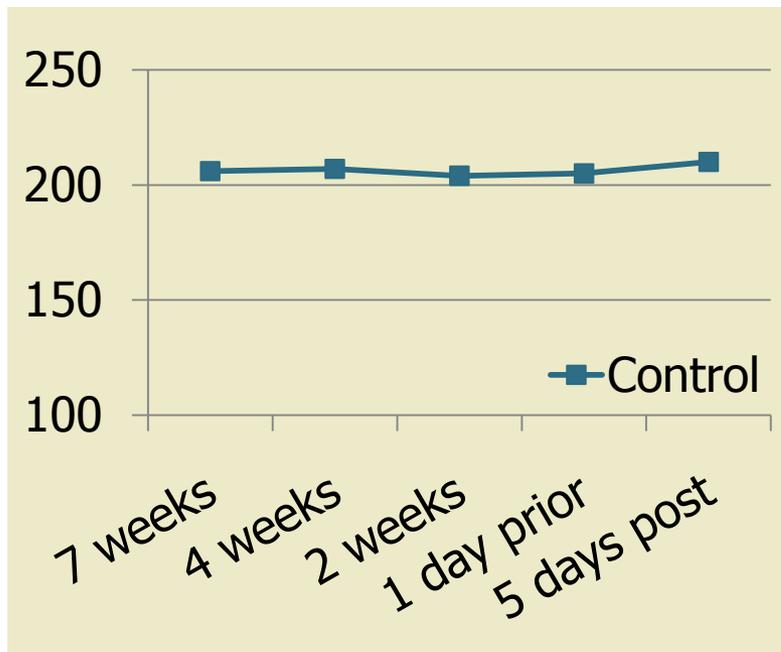
RV Diastolic Pressure
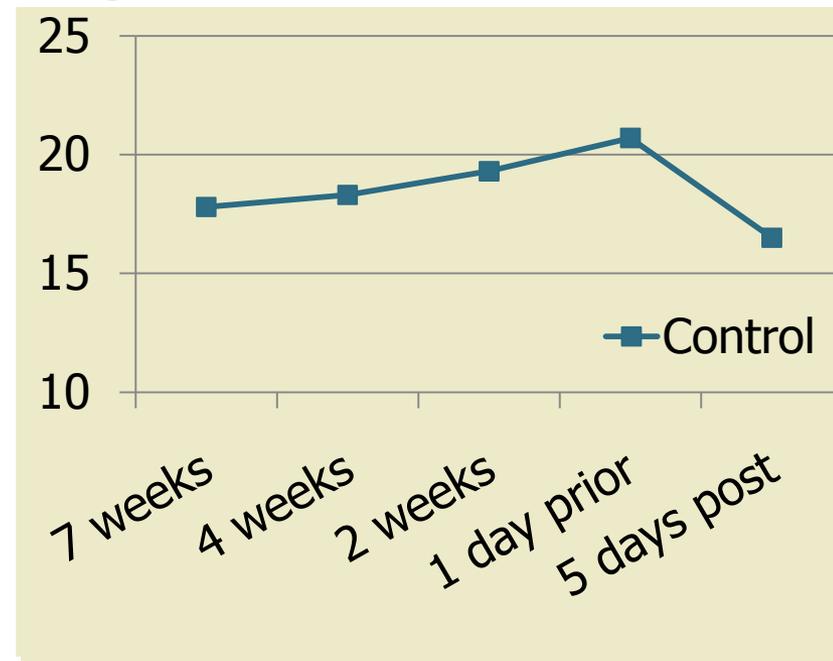
Data from the COMPASS trial

∗ = p<0.05 vs 1 day prior hospitalization

Heart Failure Events Develop Slowly

Zile et al
COMPASS Investigators
Circulation 2008
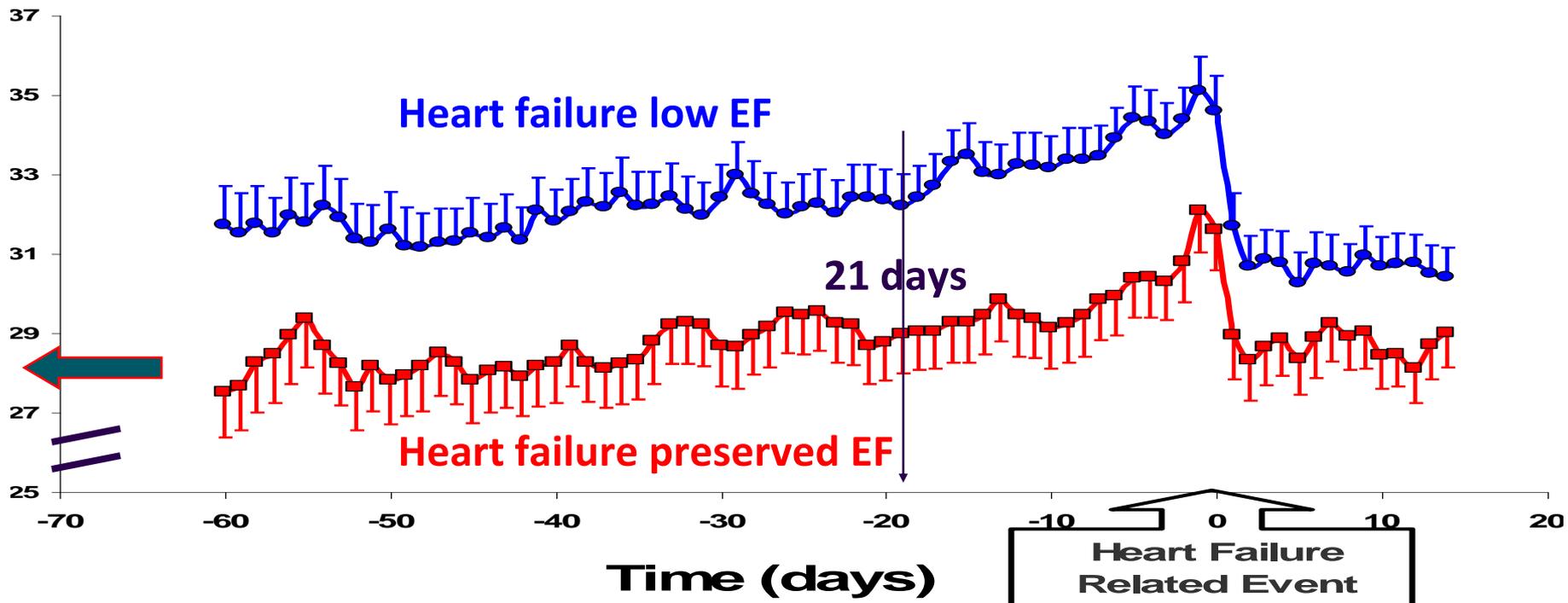
Life on a High Pressure Plateau
Is Life With High Risk

Excluding pressures 7 days before or after event
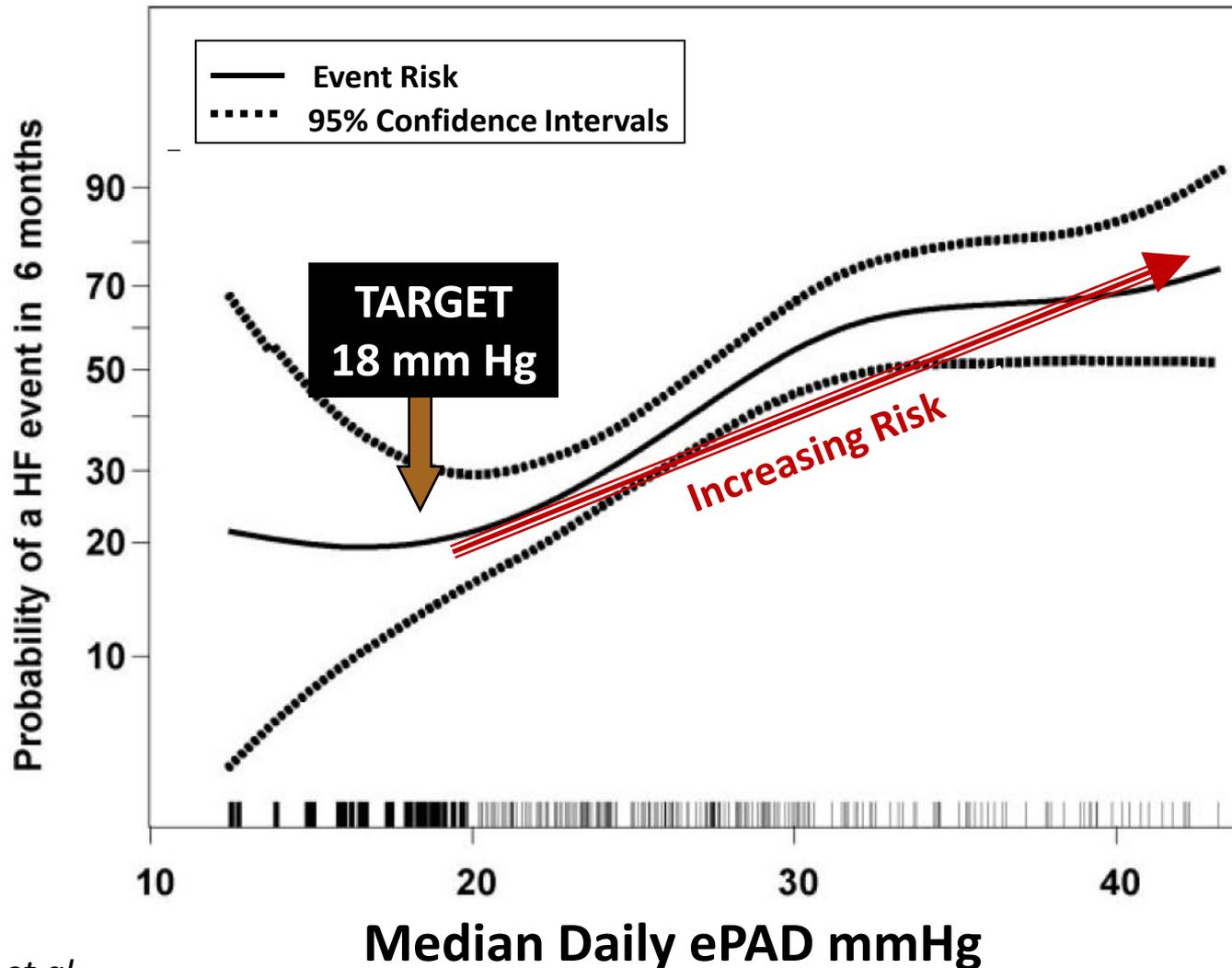
Stevenson LW, et al.
Circ Heart Fail. 2010 Sep;3(5):580-7. Epub 2010 Jun 18.

The Evolution of Pressure-Guided Therapy

- Congestion is the limiting symptom

- Cardiac output is optimized with treatment of congestion

- Relief of congestion treats the disease, not just the symptoms

- Symptoms and weights do not provide a reliable early warning system

- Seeing is relieving
  - Events are associated with increased pressures
  - HF preserved EF is more the same than different
  - Treating the peaks is not enough to prevent events

- Reduce not just peaks but also the plateau

The New Landscape
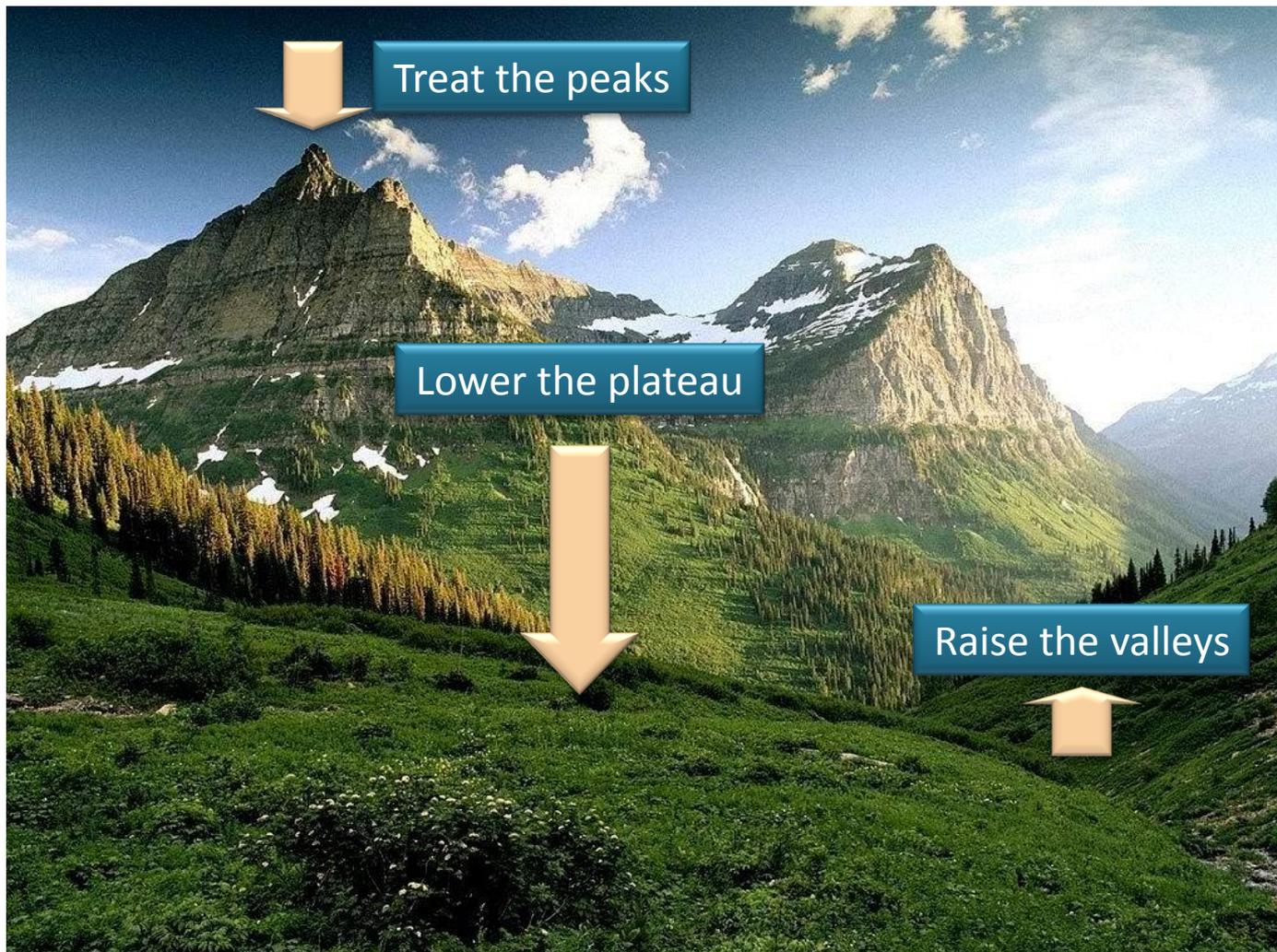
"His life is happiest who can welcome change."

— Albert Schweitzer

CHAMPION
Study Design

Philip B. Adamson, MD, FACC
Director, The Heart Failure Institute at
Oklahoma Heart Hospital

Medical Director,
Oklahoma Foundation for
Cardiovascular Research

Principal Investigator,
CHAMPION trial
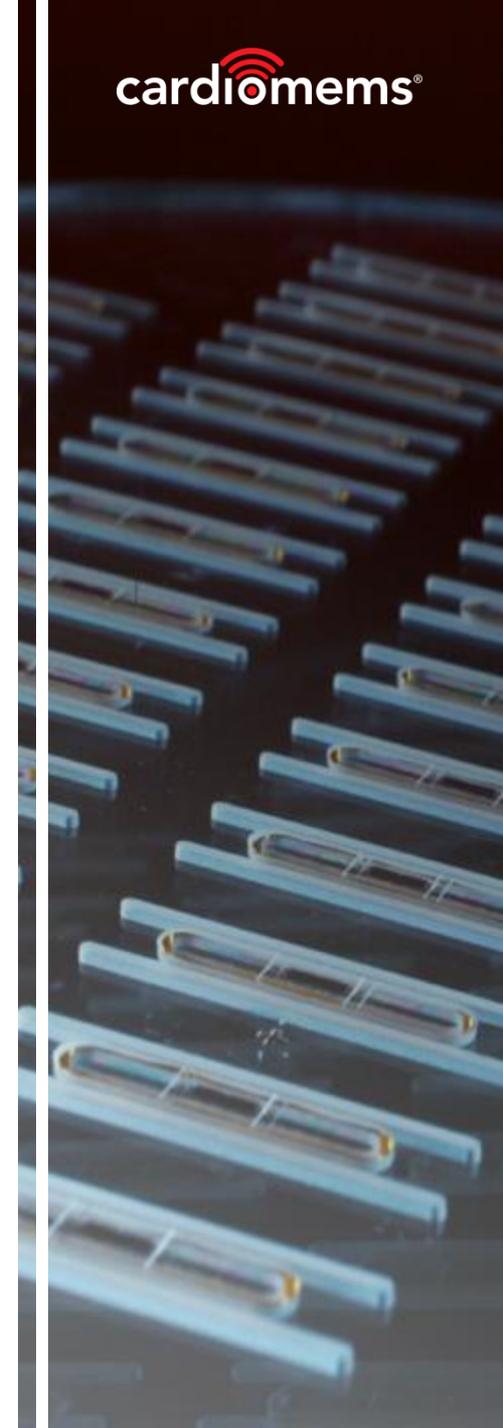
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Presentation Outline

- **Study objectives**

- Study design and endpoints

- Clinical management strategy (Appendix E)

- Study Conduct

CHAMPION Hypothesis

"The hypothesis of the CHAMPION trial is that heart failure management using pulmonary artery pressures reduces the rate of heart failure hospitalizations".

"The key to adequate testing of this hypothesis is that pressures should be used for the basis of clinical decision making"

Shift from Acute to Chronic Disease Management

Coronary Deaths

Coronary deaths are down by half…

Heart Failure Hospitalizations

But heart failure has almost tripled
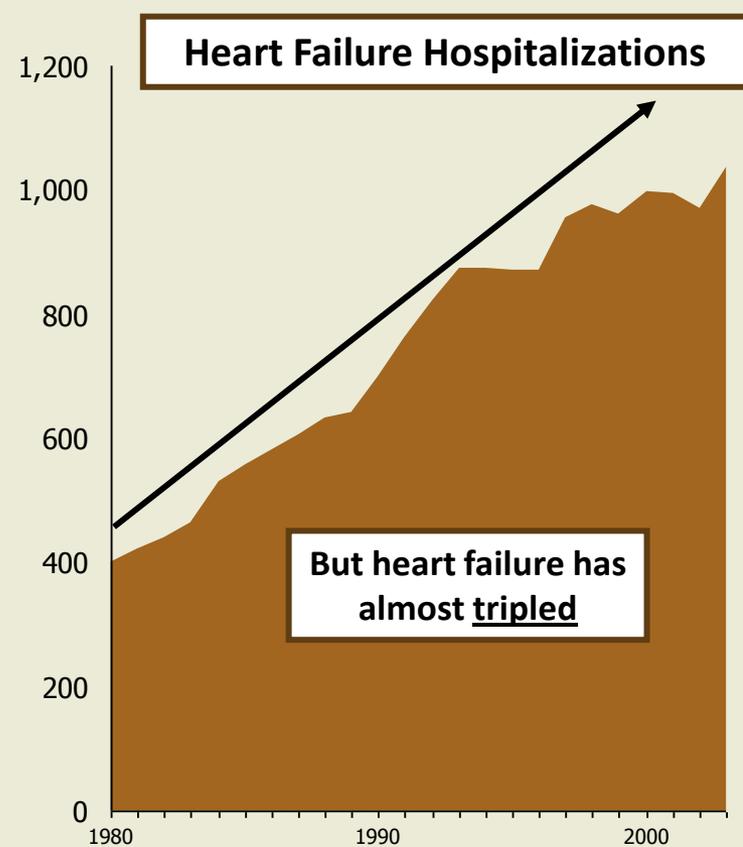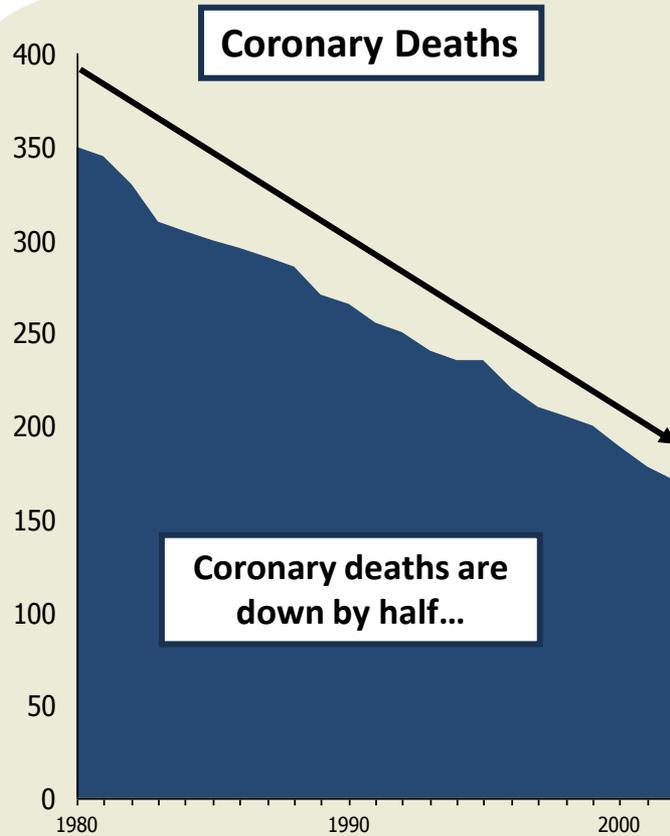
Source: National Hospital Discharge Survey, CDC/NCHS and NHLBI.

Trials of Management Strategies to Prevent Hospitalizations

	Trials	**Subjects**
Signs & Symptoms, Weights	12	2,783
Telemonitoring	3	2,789
Impedance	3	991
BNP	8	2,056
Total	**26**	**8,619**

Telemanagement:
Clinical Management Without Hemodynamics

- Tele-HF (Chaudhry SI, et al: NEJM 2010)
  - 1,653 patients randomized to telemonitoring or usual care
  - No reduction in risk of readmission or death
  - No reduction in risk of HF hospitalization

- TIM-HF (Koehler F, et al: Eur J Heart Fail 2010)
  - 710 patients randomized to remote telemedical management or usual care
  - No reduction in risk of all cause death
  - No reduction in CV death and HF Hospitalization

- TEN-HMS (Cleland JG, et al: JACC 2005)
  - 426 patients randomized to remote telemedical management or usual care
  - No reduction in days dead or hospitalized
  - No reduction in the number of hospitalizations and mortality

Hemodynamic Monitoring Without Guidelines

- COMPASS HF (Bourge RC, Abraham WT, Adamson PB, et al: JACC 2008)

  - 274 patients randomized to standard care or hemodynamic guided care

  - No protocol recommendations for treatment

  - No significant reduction in HF related events (21%, p=0.33)

- REDUCE-HF (Adamson PB, et al: Congestive Heart Failure 2011)

  - 400 patients randomized to standard care or hemodynamic guided care

  - No protocol recommendations for treatment

  - No reduction in HR related events (p=0.98)

CHAMPION

Hemodynamic Information
+
Treatment Guidelines &
Support

Significantly Improved
Clinical Outcomes

Studies in Hemodynamic Monitoring Preceding CHAMPION

Management of pressures minimizes congestion, maintains health and reduces HF hospitalizations

Managing to pressures helps maintain stable pressures

High pressures increase risk of hospitalization

Steimle, 1997

COMPASS-HF, 2008

REDUCE-HF, 2011

CHAMPION, 2011

Chronicle, 2003

HOMEOSTASIS, 2010

CardioMEMS Feasibility, 2006

Managing to pressures

E v o l u t i o n   o f   M a n a g i n g   P r e s s u r e s

Steimle AE, et al. Circulation, 1997

Chronicle: Adamson, et al JACC, 2003
Zile MR, et al. Circulation, 2008
COMPASS-HF: Bourge RC, et al. JACC, 2008
HOMEOSTASIS: Ritzema J, et al. Circulation, 2010
REDUCE-HF: Adamson PB, et al: Congestive Heart Failure 2011

CHAMPION Feasibility: Abraham WT, et al. Am Heart J, 2011
CHAMPION Design: Adamson PB, et al. J Card Fail. 2011
CHAMPION: Abraham WT, et al. Lancet, 2011

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Study Design: Prospective, Randomized, Single-blind Trial

Successful Implantation
n = 550

Treatment Group
Implant +
PAP readings +
Pressure management +
Standard of care

Randomized 1:1
Study blinded until last patient last follow-up

Control Group
Implant +
PAP readings +
No pressure management +
Standard of care

6 months　　　　**15 months**
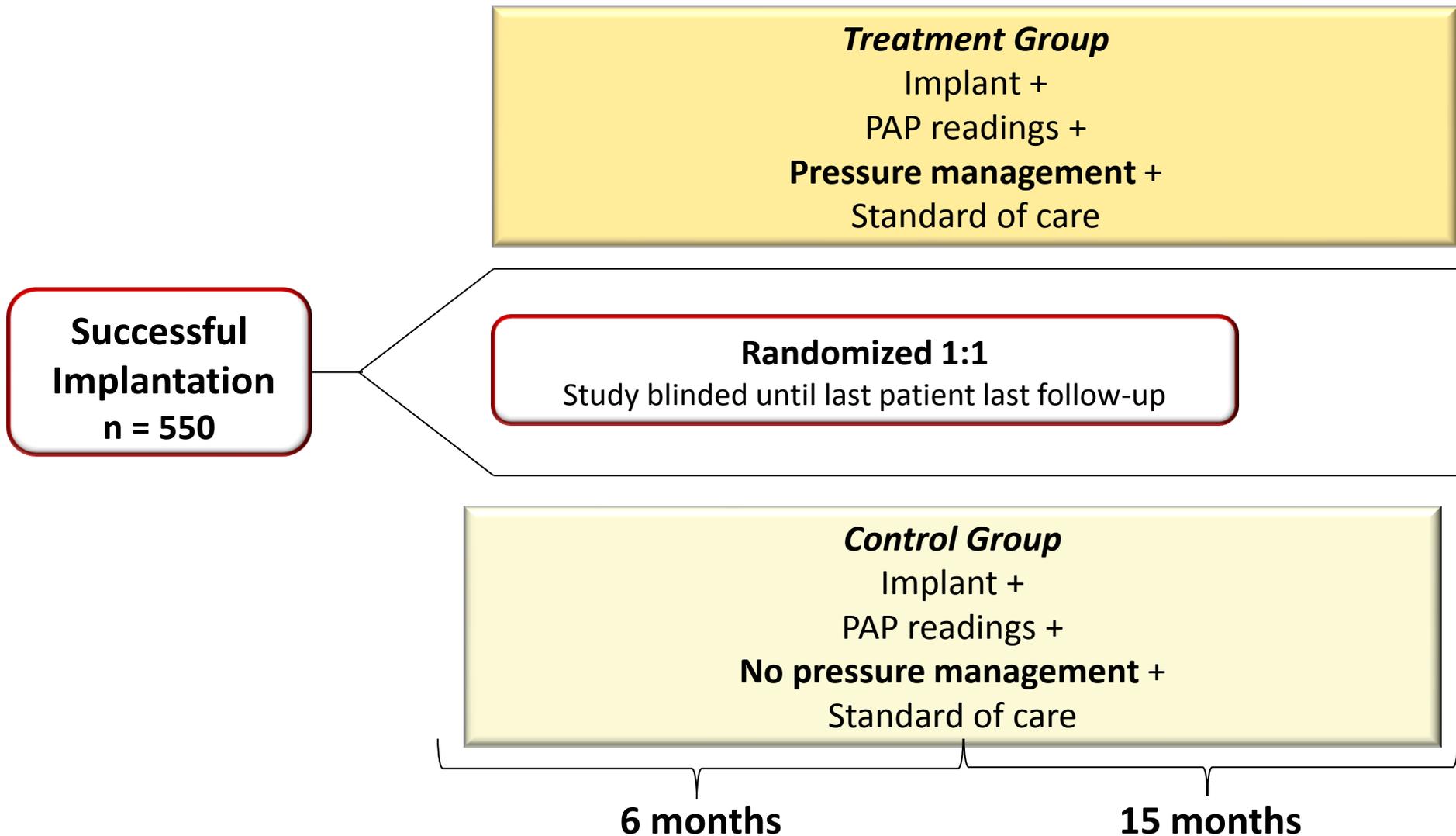
Pressure-Based Medical Management Workflow
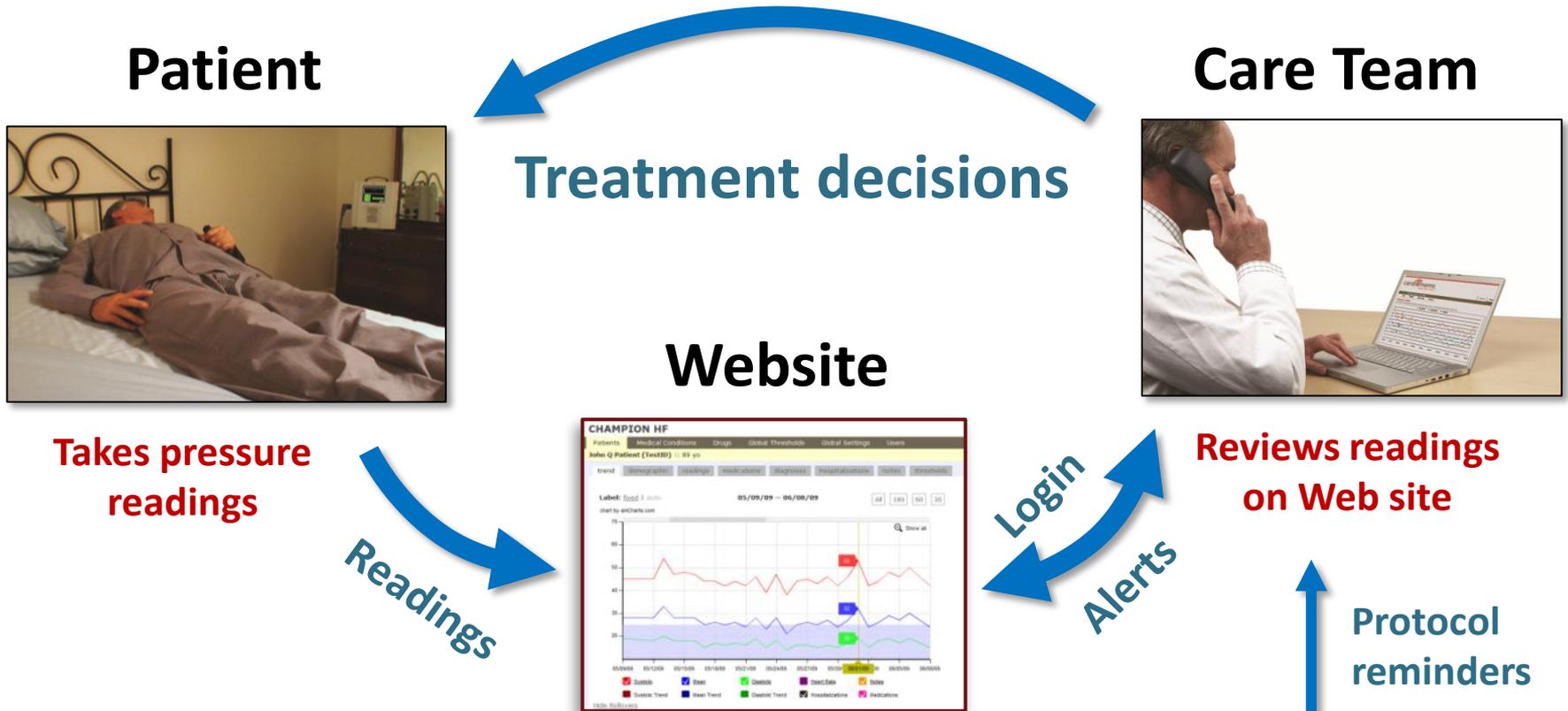
Major Inclusion Criteria

- NYHA Class III HF

- Reduced EF patients had to be on stable heart failure therapy per ACC/AHA guidelines
  - ACE/ARB, Beta Blocker and CRT therapy if indicated

- HF hospitalization within the past 12 months

- Anatomical criteria
  - PA branch diameter between 7mm - 15mm
  - distance from patient's back to the target PA <10 cm

Major Exclusion Criteria

- History of recurrent pulmonary embolism or deep vein thrombosis

- GFR <25 ml/min and nonresponsive to diuretic therapy or on chronic renal dialysis

- Major cardiovascular event (e.g., myocardial infarction, stroke) within 2 months of Screening Visit

- Known coagulation disorders

- Hypersensitivity or allergy to aspirin and/or clopidogrel

Primary Safety Endpoint

Primary Safety Endpoints

- Freedom from Device / System-related Complication (DSRC) Rate at 6 months

  H_0: P ≤ 80%
  H_a: P > 80%

- Freedom from Pressure Sensor Failure at 6 Months

  H_0: P ≤ 90%
  H_a: P > 90%

Statistical Methodology

- Exact binomial test for combined patient groups at 6 months
- O'Brien-Fleming final significance level of 0.048 (95.2% confidence interval)
- Significance of both endpoints required for positive safety results
- Sample size of 306 patients for 90% power

Primary Efficacy Endpoint

Primary Efficacy Endpoint Analysis

- Rate of HF Hospitalizations up to the 6-month Visit

H_0: $\text{Rate}_{\text{Treatment}} = \text{Rate}_{\text{Control}}$

H_a: $\text{Rate}_{\text{Treatment}} \neq \text{Rate}_{\text{Control}}$

Statistical Methodology

- Evaluated using Negative Binomial Regression

- O'Brien-Fleming final significance level of 0.048

- Sample size of **550** patients (496 for 90% power + 10% discontinuations)

Secondary Efficacy Endpoints

Endpoints evaluated hierarchically for multiplicity control

1. Change in PAP (integral of pressure curve):
     Analysis of Covariance with baseline PAP as Covariate

2. Proportion of Subjects Hospitalized for HF:
     Fisher's Exact Test

3. Days Alive Out of the Hospital (for HF):
     Wilcoxon Rank Sum Test

4. Quality of Life (Minnesota Living w/ HF Questionnaire) Total Score:
     Two-Group t-test

Presentation Outline

- Study objectives

- Study design and endpoints

- **Clinical management strategy (Appendix E)**

- Study conduct

Testing the Hypothesis

APPENDIX E: MANAGEMENT OF HEMODYNAMIC PARAMETERS

The hypothesis of the CHAMPION trial is that heart failure management using pulmonary artery pressures reduces the rate of heart failure hospitalizations. The unique nature of the implanted device allows intermittent assessment of pulmonary artery systolic, diastolic and mean pulmonary artery pressures. The key to adequate testing of this hypothesis is that pressures should be used for the basis of clinical decision making in addition to symptoms, weights or physical examination (traditional markers of volume).

Guidelines for managing heart failure using pulmonary artery pressures

The CHAMPION trial will <u>differ</u> from previous hemodynamic monitoring studies in that <u>specific</u> recommendations will be made to utilize pressures in heart failure management including use of diuretics and vasodilators.

In addition to these specific guidelines, the investigator should also incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.

Elevated PA Mean Pressure Treatment Strategies in Protocol (Appendix E)

Elevated PA Mean Pressure PA mean trending above the normal hemodynamic range

Add or increase diuretic
- increase/add loop diuretic
- change loop diuretic
- add thiazide diuretic
- IV loop diuretic

*Minimum weekly review of PA mean trends

Add or increase vasodilators
- add or increase nitrate
- add or increase hydralazine
- increase ACE/ARB or BB

Re-evaluate PA pressures 2-3 days per week until PA pressures stabilize

Hospitalization if unresponsive to outpatient medical therapy

If PA Pressures remain elevated evaluate other etiologies i.e. dietary indiscretion, sleep apnea, etc.

Ultimate treatment decisions were made by the Investigator

Ensuring a Uniform High Level Standard of Care In Both Study Arms

Extensive support and training program was provided ensure standardized HF care for all patients

- 7 investigator meetings

- 56 site/PI conference calls

- 47 newsletter issues

- HF management materials

- Comprehensive training program

- Summary of HF medications and interactions in every patient binder

Presentation Outline

- Study objectives

- Study design and endpoints

- Clinical management strategy (Appendix E)

- **Study conduct**

CHAMPION Trial Milestones

FDA, National PI's, & CardioMEMS discuss Pivotal Study Design

1st CHAMPION Patient Enrolled

550th CHAMPION Patient Enrolled

550th Patient Reaches 6 Month

2006 2007 2008 2009 2010 2011

FDA Approved Enrollment:
20 sites/70 pts → 75 sites/550 pts

Clinical PMA Submission
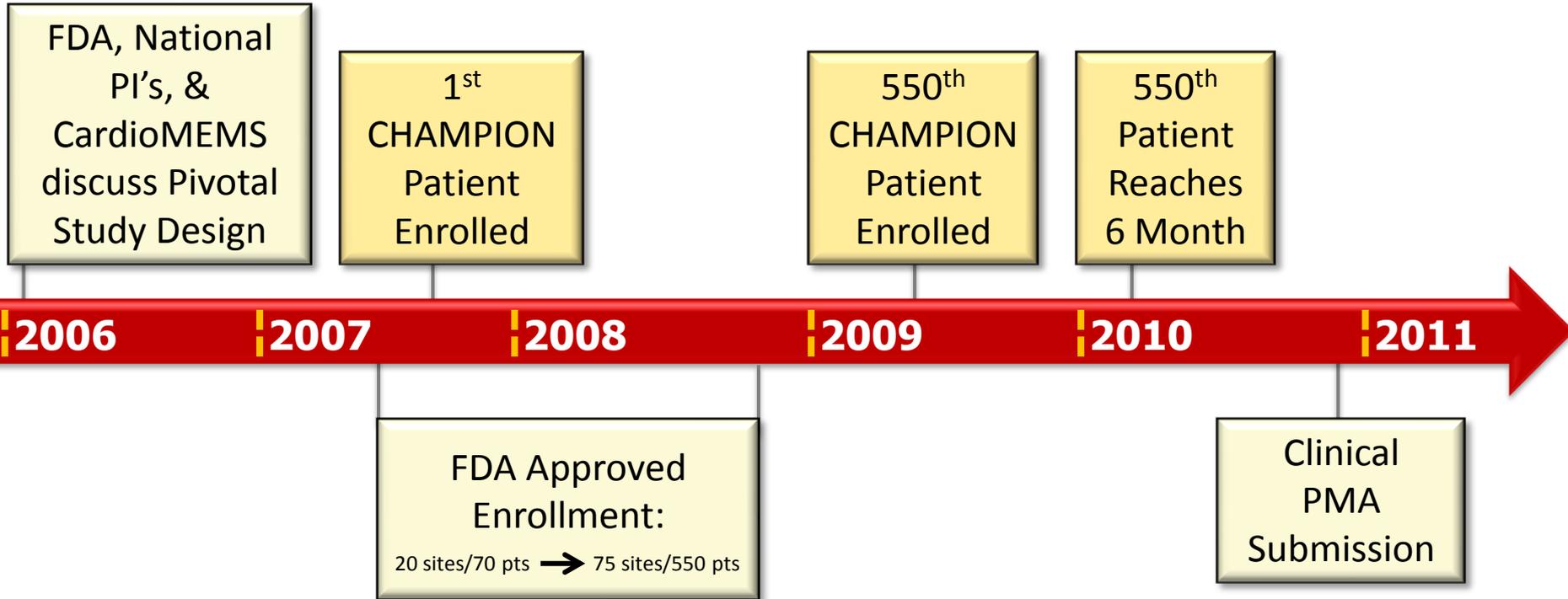
Clinical Trial Oversight
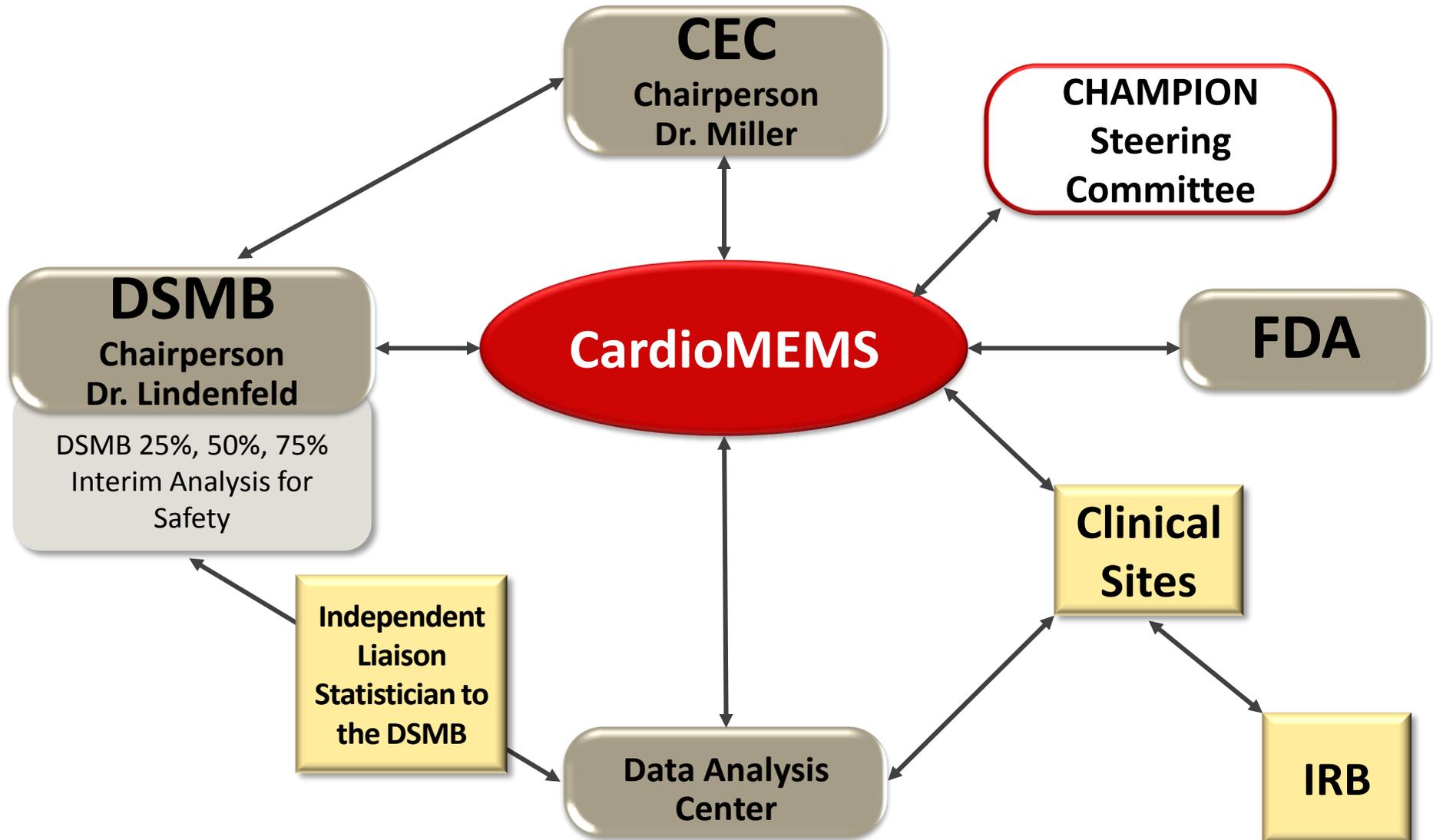
Sponsor and Principal Investigator Input to Ensure Scientific Soundness

- Rigorous testing of trial hypothesis
  - Uniformity of pressure based treatment strategies
  - Protocol designed to ensure investigator compliance

"Consultation with the national PI's is encouraged to optimize the success of medical management of PA pressures"

- Included in IDE Submission June, 2007 – approved September, 2007

- Reviewed during FDA Bio Research Audit of CardioMEMS – March 2011
  - No observations issued

cardioMEMS SENSING WHAT'S VITAL™	Page 1 of 9	
Title: CHAMPION SUBJECT QUALIFYING and MEDICAL MANAGEMENT	**Department**	Clinical Operations
	Standard Operating Procedure Number	SOP-000105
	Rev. Number	00

I. **OBJECTIVE**

This procedure describes the CardioMEMS process for overseeing subject qualification and the medical management of treatment patients in the CHAMPION Clinical Trial. CardioMEMS, the study sponsor, must ensure all subjects meet inclusion and exclusion criteria. Furthermore, CardioMEMS must ensure appropriate medical management of patients in the treatment arm of the clinical trial according to the protocol.

CardioMEMS Automated Pressure Email Alert

Dear Philip Adamson, MD

A new reading has come in for your patient, 01-012 PAM which violated the alert threshold set up for "Mean Pressure above 20.0 mmHg". The reading was taken on 07 Dec 07:12 CST.

Systolic: 29
Diastolic: 18
Mean: 22
Heart Rate: 91

Pressure waveform is attached.

To view more information on the readin~~~
below or copy+paste it into your web br~~~
http://champion.cardiomems.com/

Thank you,
CardioMEMS Alert System
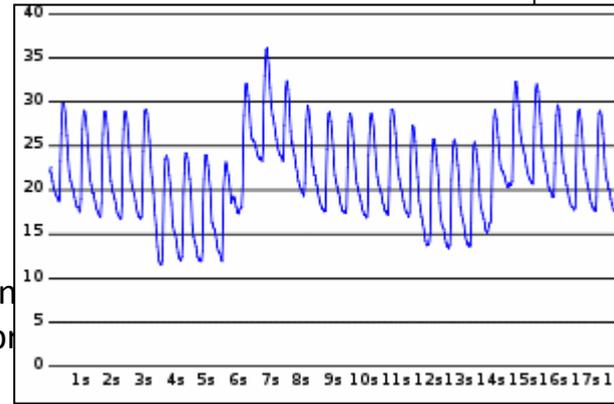
CardioMEMS Automated Review

Trends/Unusual Readings Flagged

Reading Reviewed by Clinical Nurse

Possible **Inquiry** or **Recommendation** Email Sent

Care Provider

Pressure Based Medication Changes (Appendix E)

Pressure Trend Initiated Emails

Inquiry Email

From: Susan Neville
Sent: Mon 2/9/2009 1:32
To: ▮▮▮
Cc: ▮▮▮ ▮▮▮; ⊞ Clinical Nurses
Subject: ▮▮▮

▮▮▮

I want to make sure you and x are aware of the **elevated PA pressures** for subject x. Our records show this PCWP at implant was 36. Do you know if he was treated post-implant when he was in the hospital? The only medication changes we have in our records are the addition of ASA and Plavix, post-implant. Would you please confirm if these have been additional changes and also let me know the plan for this patient?

Please remember it is vital we adequately test the hypothesis of the trial, that pressures should be used for the basis of clinical decision making in addition to traditional markers of volume.

Recommendation Email
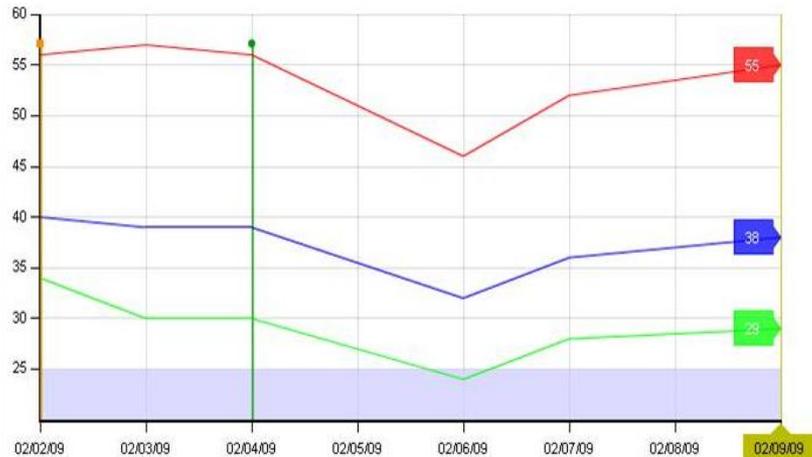
From: Pam Cowart
Sent: Mon 7/28/2008 4:2▮
To: ▮▮▮
Cc:
Subject: Champion Trial- Medical Management of Su▮▮

▮▮▮

Just wanted to alert you to the **upward trend** of Subject x's PA Pressures over the last week with a PAM 35 today. I would guess that weekend dietary indiscretion maybe a contributing factor.
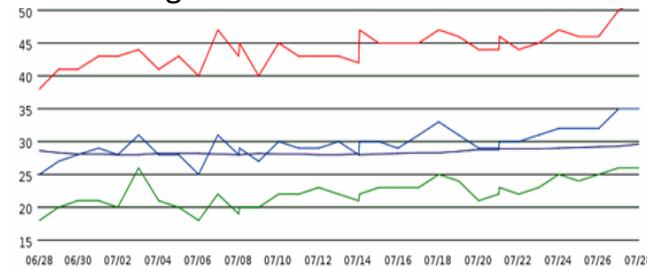
My records indicate the subject is currently on the following CV medications:
Cozaar 25 QD
Bystolic 10 QD
Aldactone 12.5 QD
Imdur 30 am, 60 pm BID
Lasix 80 BID
Zaroxolyn PRN (when did the subject last use this ? ▮▮
KCL 10 BID
Norvasc 5 QD
Ranexa 500 BID
Anticoaguation: Plavix, Coumadin, ASA

Based on Protocol (Appendix E) & ACC/AHA Heart Failure Guidelines

Please advise of any medication adjustments or treatments made in response to patient's pressures. If it is increased volume from **dietary indiscretion**, patient may just need a few days of increased **Lasix or PRN Thiazide.** If volume not a concern consider uptitrating **ARB, Nitrate** or adding **Hydralazine** to current regimen.

*Data not yet reviewed by FDA.

Pressure Readings → Investigator Reviews → Recommendation Emails
6 Months
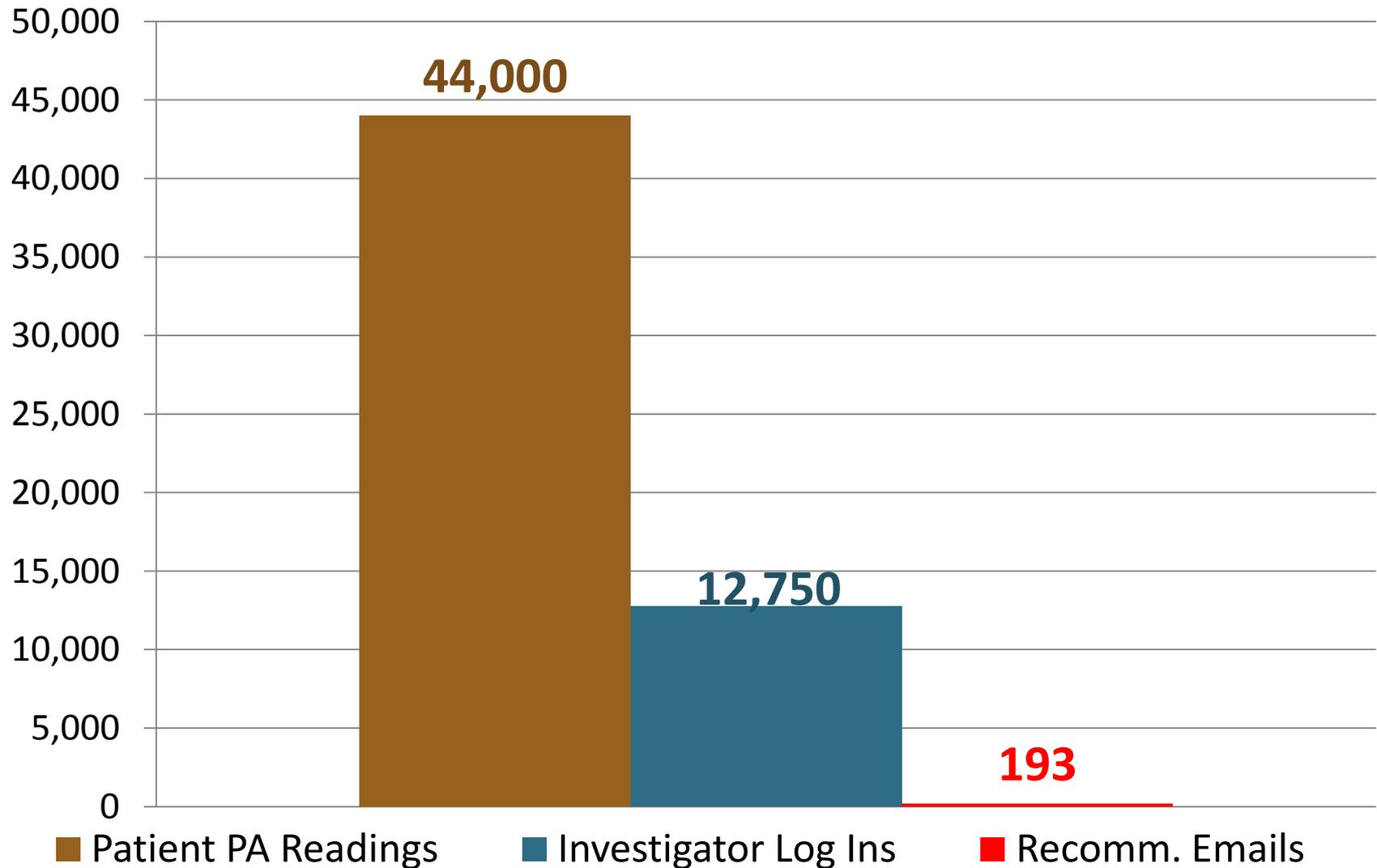
*Data not yet reviewed by FDA.

Application of PA Pressure Based HF Management Guidelines

Elevated PA Pressure
PA mean elevated at or above the normal hemodynamic range

Treat elevated PA pressures at baseline

Add or increase diuretics or vasodilators
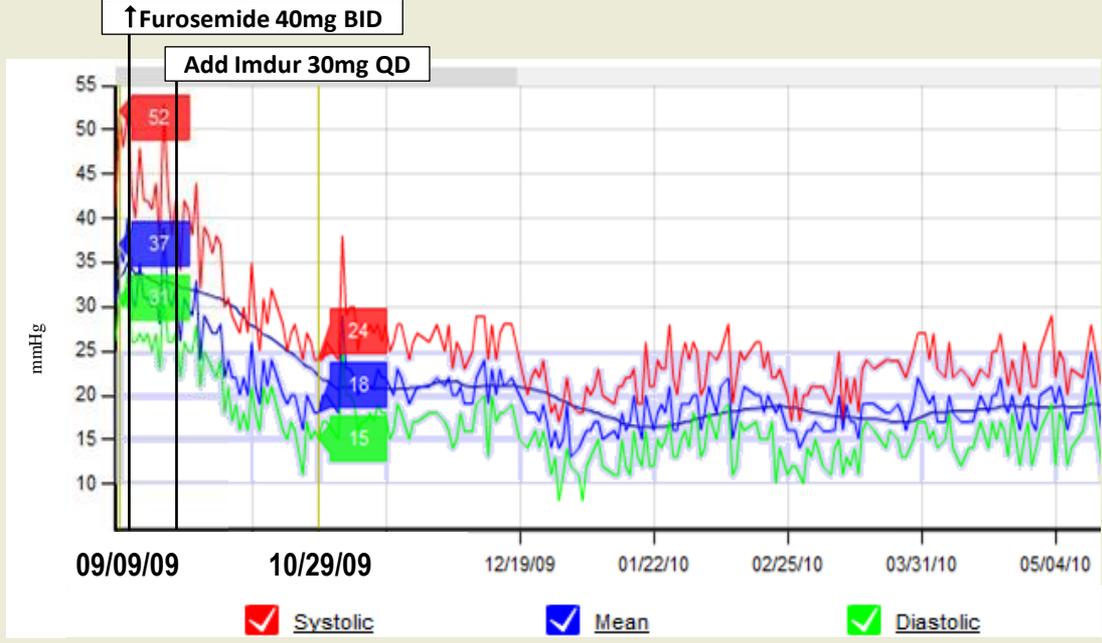
Treat PA mean trending above normal hemodynamic range

Add or increase diuretics or vasodilators

↑Furosemide 40mg BID

Add Imdur 30mg QD

Systolic   Mean   Diastolic

Add HCTZ 12.5 mg BID

↑Hydralazine 25mg TID
↑ Lasix 40mg BID

↑ Lasix 80mg BID

Systolic   Mean   Diastolic
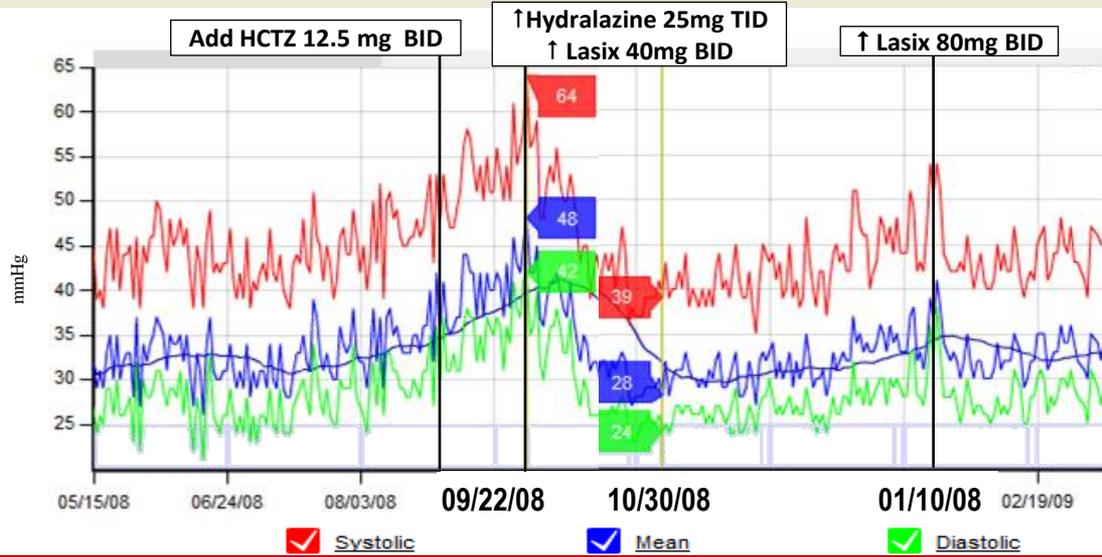
The CHAMPION Trial Was Rationally Designed

- Builds on extensive history and clinical investigation into hemodynamic monitoring of HF patients

- Combines hemodynamic information + treatment guidelines & support

- Represents real world with broad patient population

- Differs from previous hemodynamic studies in making specific pressure based management recommendations

- Designed with extensive oversight in collaboration with the FDA

CHAMPION
Clinical Trial Results

William T. Abraham, MD, FACP, FACC, FAHA, FESC
Professor of Medicine, Physiology, and Cell Biology

Chair of Excellence in Cardiovascular Medicine

Director, Division of Cardiovascular Medicine

Deputy Director, Davis Heart and Lung Research Institute

The Ohio State University

Principal Investigator, CHAMPION trial

cardiomems®
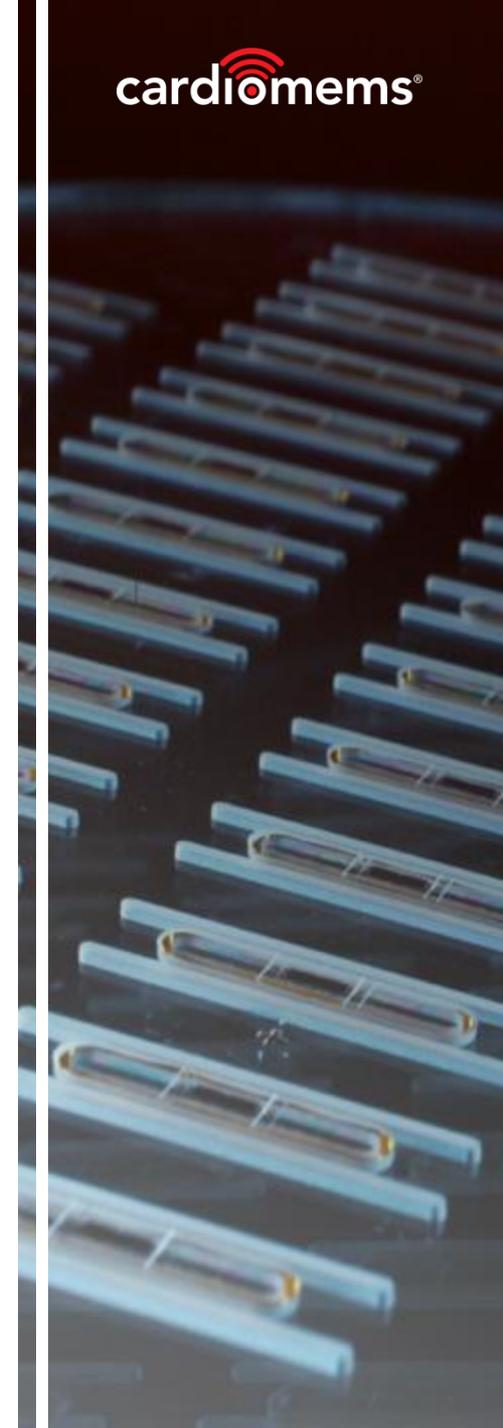
Participating Sites in CHAMPION Trial

● 49 Community hospitals   ▲ 15 Academic sites

436 (79%) Subjects   114 (21%) Subjects

Patient Disposition
Up to 6 Months

Medical Chart Screen
n=723

Chart Screen Failures
n=98

Screening Visit
n=625

Screen Failures
n=50

Right Heart Catheterization
n=575

Consented Not Implanted n=25
(followed for 30 days for safety)
(10) Anatomical exclusion criteria
(9) RHC not possible
(6) Unsuccessful implant attempts
– Severe chronic cough and difficulty maintaining guide wire position
– Pre-existing PE/DVT
– 2 Transient Arrhythmias
– 2 Sensor did not release; successfully removed

Patient Disposition
Up to 6 Months

**Implanted and
Randomized/Blinded 1:1
n=550**

**Treatment
n=270**

**Control
n=280**

26 EXITED prior to 6 Months
  (15) Deaths
  (4) Noncompliance
  (3) Withdrew consent
  (3) Investigator decision
  (1) Enrolled in investigational
      VAD study

26 EXITED prior to 6 Months
  (20) Deaths
  (1) Noncompliance
  (3) Withdrew consent
  (1) Investigator decision
  (1) Lost to follow-up

**6 Mo. Visit
n=244**

**6 Mo. Visit
n=254**

Baseline Patient Characteristics

	Treatment (n=270)	Control (n=280)	p-value
Demographics			
Age (yr)	61 (22 - 88)	62 (24 - 90)	0.59
Gender (% Female)	28%	27%	0.77
Race (% non-Caucasian)	27%	27%	0.92
BMI (kg/m^2)	31 (18 - 54)	31 (16 - 74)	0.75
Ejection Fraction (% ≥ 40%)	23%	20%	0.53
Ischemic Cardiomyopathy	59%	62%	0.43
History of Myocardial Infarction	50%	49%	0.93
CRT/CRT-D Device	34%	35%	0.72
ICD Device	33%	35%	0.59
Baseline PA Mean Pressure ±SD	31 ±11	32 ±11	0.56
Comorbidities			
Hypertension	77%	79%	0.61
Coronary Artery Disease	67%	72%	0.23
Diabetes Mellitus	48%	50%	0.73
Atrial Flutter/Fibrillation	44%	48%	0.39
COPD	28%	30%	0.71
Chronic Kidney Disease	20%	19%	0.91

Heart Failure Drug Therapy at Baseline

	Treatment (n=270)	Control (n=280)	All Patients (n=550)	p-value
ACE/ARB	76%	79%	78%	0.36
Beta Blocker	90%	91%	91%	0.66
Aldosterone Antagonist	43%	41%	42%	0.55
Nitrate	24%	20%	22%	0.30
Hydralazine	13%	12%	12%	0.61
Diuretic-Loop	92%	92%	92%	0.99
Diuretic-Thiazide-Standing	11%	12%	12%	0.69
Diuretic-Thiazide-PRN	7%	6%	7%	0.74

- Reduced EF: OPT neurohormonal therapy per ACC/AHA guidelines

- Preserved EF: 21% of CHAMPION patients, no medication guidelines

- No differences between the treatment and control groups at baseline

Pitt B et al. N Engl J Med 2003
Swedberg K et al. Lancet 2010
Velduisen, DJ, et al. Circulation, 2011

CHAMPION Baseline HF Medication Doses Compare Favorably to Major Clinical Trials

- Distinction between "maximal" and "optimal" dose
  - ➤ Maximal - largest dose that can be utilized in treating patients
  - ➤ Optimal - highest tolerated dose for a given patient

Drug Class	Medication	CHAMPION Dose at Baseline (mg)	HF Trials Mean Dose Achieved (mg)	Trial
ACE-I	Enalapril	20.8	16.6	SOLVD
Beta-Blocker	Carvedilol	30.1	25	SHIFT *
			37	COPERNICUS
Aldosterone Antagonist	Spironolactone	30.6	26	RALES
Vasodilator	Hydralazine	121.4	142.5	A-HeFT
	Nitrate	58.9	76	

*Non-forced titration

Both Primary Safety Endpoints Met

Safety endpoints based on 575 patients

- 550 randomized + 25 Consented Not-Randomized (CNR), not implanted
- Objective Performance Criteria (OPC) based upon complication and failure rates for other HF monitoring devices and similar to OPCs accepted by the FDA

1. **Freedom from Device/System Related Complications (DSRC) 567/575 (98.6%, lower 95.2% CL = 97.3%)**
   - Compared to Pre-specified OPC of 80%, p<0.0001

2. **Freedom from Pressure Sensor Failures 550/550 (100.0%, lower 95.2% CL = 99.3%)**
   - Compared to Pre-specified OPC of 90%, p<0.0001

Primary Efficacy Endpoint Met

	Treatment (n=270)	Control (n=280)	Relative Risk Reduction	p-value
# of HF Hospitalizations (Rate for 6 months)	84 (0.32)	120 (0.44)	**28%**	**0.0002**

p-value from negative binomial regression

• Number needed to treat (NNT) = 8

Cumulative HF Hospitalizations Reduced
At 6 Months and Full Duration

≤ 6 Months 28% RRR, p = 0.0002

> 6 Months 45% RRR, p < 0.0001

Study Duration 37% RRR, p < 0.0001

Treatment (158 HF Hospitalizations)
Control (254 HF Hospitalizations)

Y-axis: Cumulative Number of HF Hospitalizations (0, 20, 40, 60, 80, 100, 120, 140, 160, 180, 200, 220, 240, 260, 280)

X-axis: Days from Implant (0, 90, 180, 270, 360, 450, 540, 630, 720, 810, 900)

No. at Risk
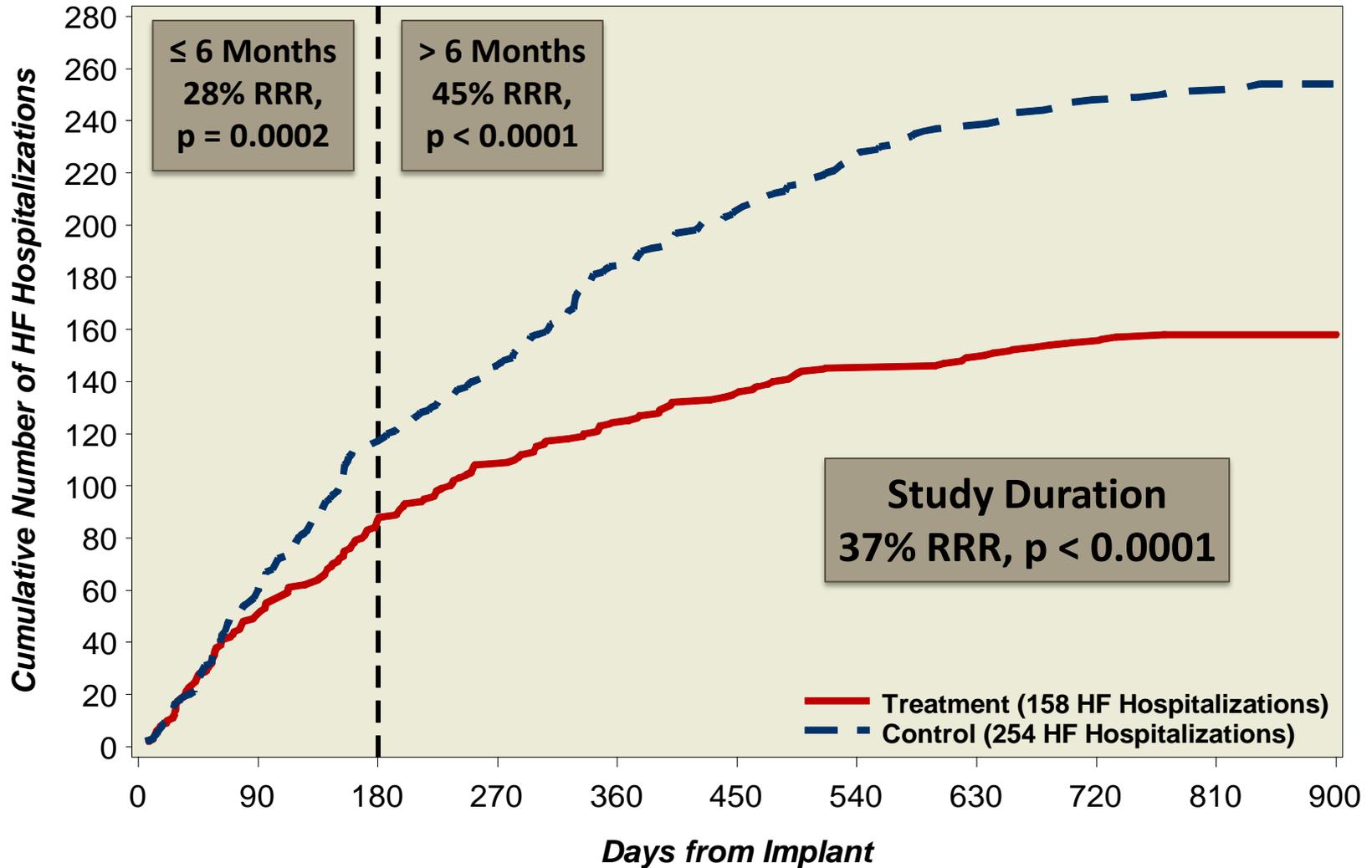
	0	90	180	270	360	450	540	630	720	810	900
Treatment	270	262	244	210	169	131	108	82	29	5	1
Control	280	267	252	215	179	137	105	67	25	10	0

All Secondary Efficacy Endpoints Met
Tested in Hierarchical Fashion

	Treatment (n=270)	Control (n=280)	p-value
Change from Baseline in Mean Pulmonary Artery Pressure, mean AUC (mmHg-days)	-155.7	33.1	**0.0077**

Baseline = Average pressure in first week after implant
p value from analysis of covariance

All Secondary Efficacy Endpoints Met
Tested in Hierarchical Fashion

	Treatment (n=270)	Control (n=280)	p-value
Change from Baseline in Mean Pulmonary Artery Pressure, mean AUC (mmHg-days)	-155.7	33.1	0.0077
Proportion of Patients Hospitalized for HF, #(%)	55 (20%)	80 (29%)	**0.0292**

p value from Fisher's exact test

All Secondary Efficacy Endpoints Met
Tested in Hierarchical Fashion

	Treatment (n=270)	Control (n=280)	p-value
Change from Baseline in Mean Pulmonary Artery Pressure, mean AUC (mmHg-days)	-155.7	33.1	0.0077
Proportion of Patients Hospitalized for HF, #(%)	55 (20%)	80 (29%)	0.0292
Days Alive Outside the Hospital for HF, mean	174.4	172.1	**0.0280**

p value from Wilcoxon rank sum test

Days Alive Outside the Hospital Difference
Treatment – Control at 6 Months and 15 Months (Study Duration)

All Secondary Efficacy Endpoints Met
Tested in Hierarchical Fashion

	Treatment (n=270)	Control (n=280)	p-value
Change from Baseline in Mean Pulmonary Artery Pressure, mean AUC (mmHg-days)	-155.7	33.1	0.0077
Proportion of Patients Hospitalized for HF	55 (20%)	80 (29%)	0.0292
Days Alive Outside the Hospital for HF, mean	174.4	172.1	0.0280
Quality of Life (Minnesota Living with HF Questionnaire), mean	45.2	50.6	**0.0236**

p value from two-group t-test

Pre-specified Subgroup Analysis
Rate of HF Hospitalizations by Baseline Ejection Fraction
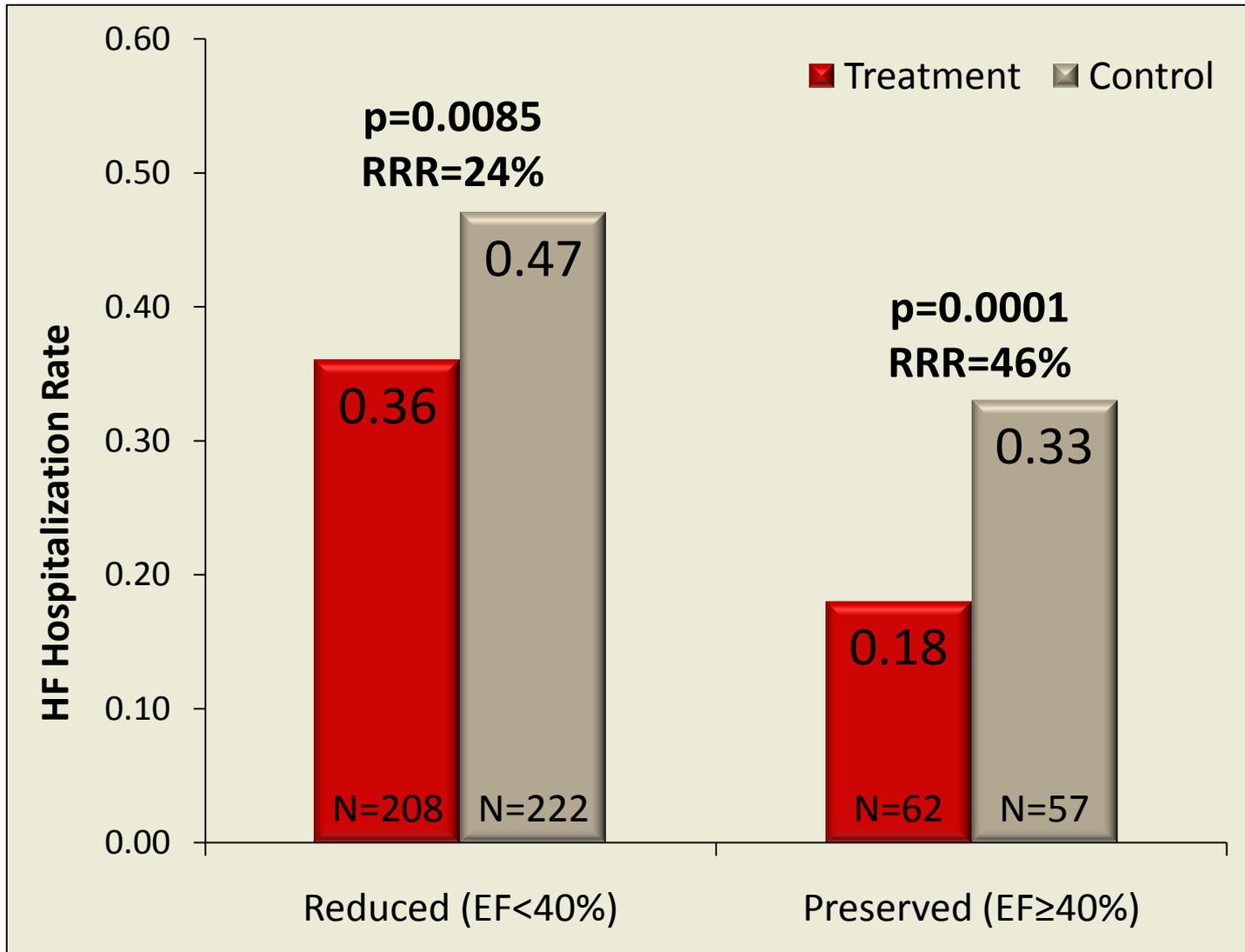
p-value from two-group t-test

Freedom from HF Hospitalization or Death in <u>Females</u>
Over Full Study Duration

*P-values calculated using Log Rank Test

HR = 0.76 (0.46-1.27), p = 0.30

Treatment (27 Subjects with at least 1 HF Hospitalization or Death)
Control (32 Subjects with at least 1 HF Hospitalization or Death)

Days from Implant
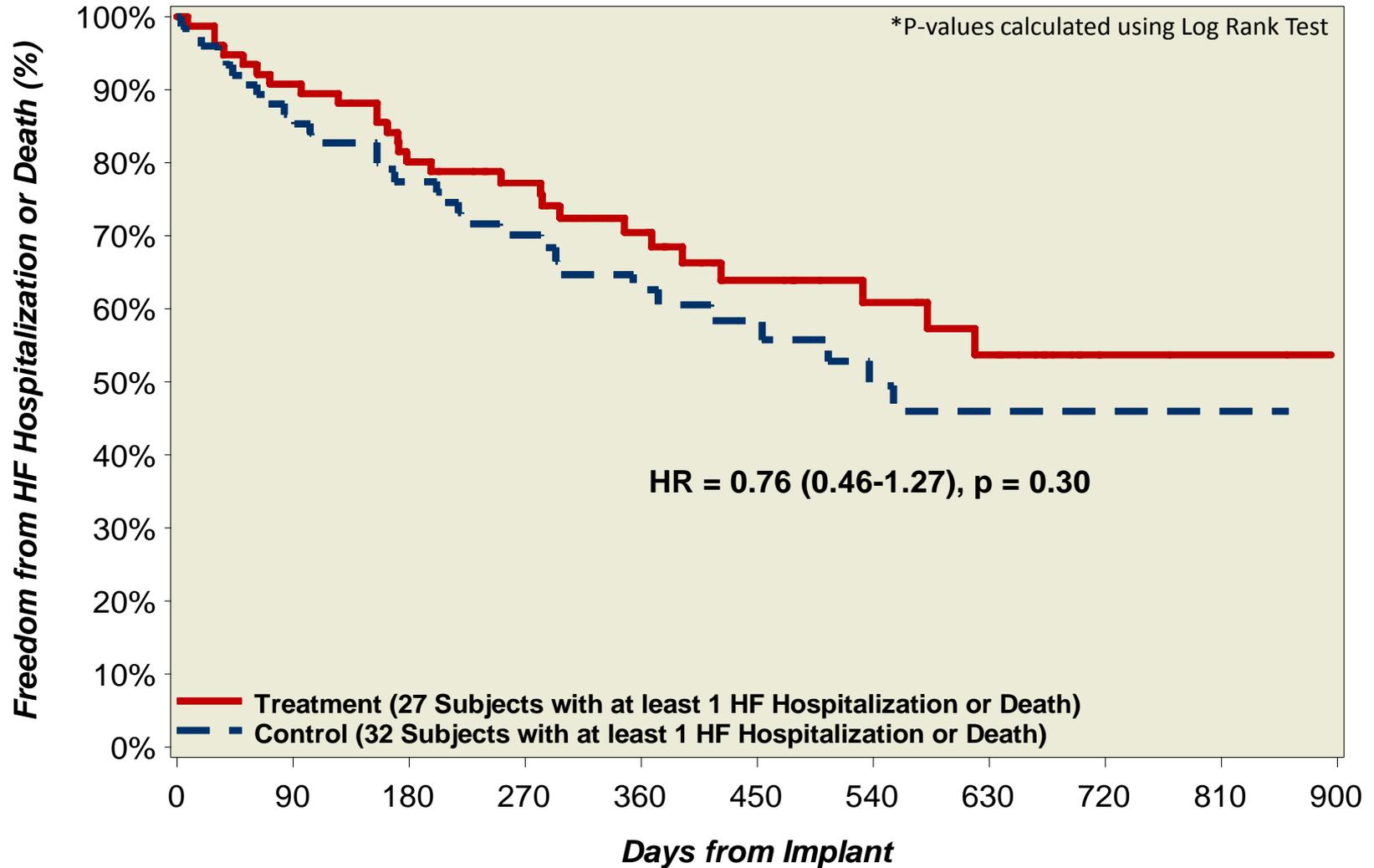
No. at Risk											
Treatment	76	69	59	50	36	26	20	15	3	2	0
Control	75	65	56	39	31	22	14	10	2	2	0

Anticipated Adverse Events Summary

Investigator Reported Anticipated Adverse Events (81)

- Reported regardless of causality and thus uses the broadest definition
- Majority not device or procedure related
- No differences between the treatment and control groups.

Anticipated AE	Treatment N=270	Control N=280	All Patients N=550
	# Events	# Events	# Events
Infection	16	12	28
Arrhythmias	16	9	25
Bleeding	9	10	19
Hematoma	4	3	7
Thrombus	2	0	2
Air Embolism	0	0	0
Delayed Wound Healing	0	0	0
Valve damage	0	0	0

Device and Procedure Related Adverse Events

Investigator Reported

Anticipated
(81)

All Other Adverse Events
(1770)
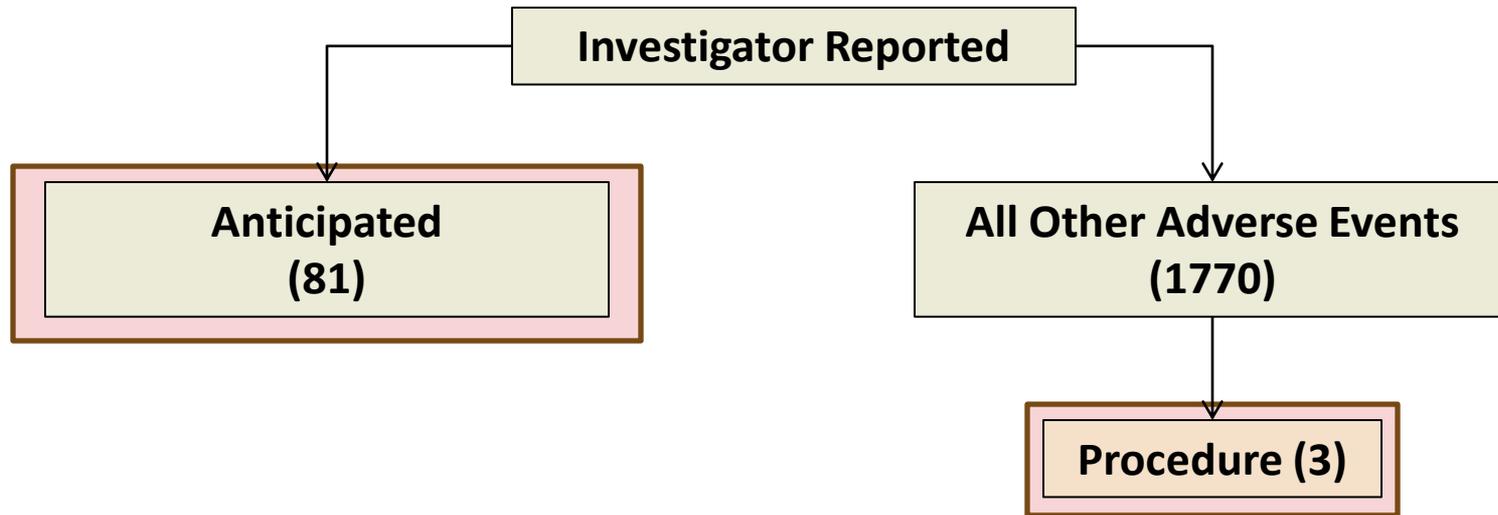
Procedure (3)

FDA calculated device and procedure related
adverse event rate:

84 events in 72 patients, rate = 13.1%

Device and Procedure Related Adverse Events

Device/Procedure Related Events	DSRCs	Procedure Related	Device Related
CEC-Adjudicated	8	7	1
Investigator Reported only			16
Post hoc FDA analysis		2	
Totals	**8**	**9**	**17**

Adverse Event Rate
(34/575) = 5.9%

Device/System Related Complications (DSRC)
Details of CEC adjudications

Adjudication	Complication	Days after implant	Description and Therapy	Outcome
Definitely	Sensor did not fully deploy	During Implant	Sensor remained attached to delivery catheter. **Therapy:** sensor removed with snare during same procedure. Patient discharged next day	**Recovered without sequela**
Definitely*	In-situ thrombus	14	CTA revealed a small thrombus in a non-sensor PA branch secondary to over-inflation of the Swan-Ganz balloon. Thrombus not associated with sensor. **Therapy:** adjusted anticoagulation	**Recovered without sequela**
Possibly*	Hemoptysis	During Implant	Chronic cough exacerbated during implant. Bronchoscopy revealed well formed thrombus, in non-implant lung, positive for Klebsiella. **Therapy:** irrigation, suction, antibiotics	**Recovered without sequela**
Possibly	Atypical Chest Pain	1	ECG normal and isoenzymes negative. **Therapy:** nitrates and analgesics	**Recovered without sequela**
Possibly	TIA	8	History of Afib, INR subtherapeutic. **Therapy:** warfarin adjusted to obtain therapeutic INR	**Recovered without sequela**
Possibly	Arterial embolism	10	History of A-Fib, INR was subtherapuetic; Right arm arterial thrombus. **Therapy:** thrombectomy and adjusted anticoagulation	**Recovered without sequela**
Possibly	Sepsis	1	HIV, Hep C, worsening respiratory distress, hemodynamic instability, sepsis. **Therapy:** antibiotics, inotropes, nebulizers	**DNR; care withdrawn**
Possibly	Atrial Dysrhythmia	1	Arrhythmia lead to worsening cardiopulmonary status. **Therapy:** amiodarone, diuretics, dopamine	**DNR; care withdrawn**

*reported by Investigator as SADE

Summary of SAEs in Randomized Patients
Up to 6 Month Follow-up Visit

	Treatment (n=270)	Control (n=280)
# of Patients(%)	121 (44.8%)	155 (55.4%)
# of Events	339	385
System Organ Class	# of Events	# of Events
Cardiac disorders	144	187
Respiratory, thoracic and mediastinal disorders	26	31
Infections and infestations	27	24
Vascular disorders	21	16
Renal and urinary disorders	19	13
Metabolism and nutrition disorders	16	13
Nervous system disorders	16	20
Gastrointestinal disorders	18	19
General disorders & administration site conditions	10	15
Surgical and medical procedures	11	13

Freedom from Death
Up to 6 Month Follow-up

*p-value from log-rank test

HR = 0.77 (0.40-1.51), p = 0.45

Treatment (15 Deaths)
Control (20 Deaths)

Freedom from Death (%)

Days from Implant
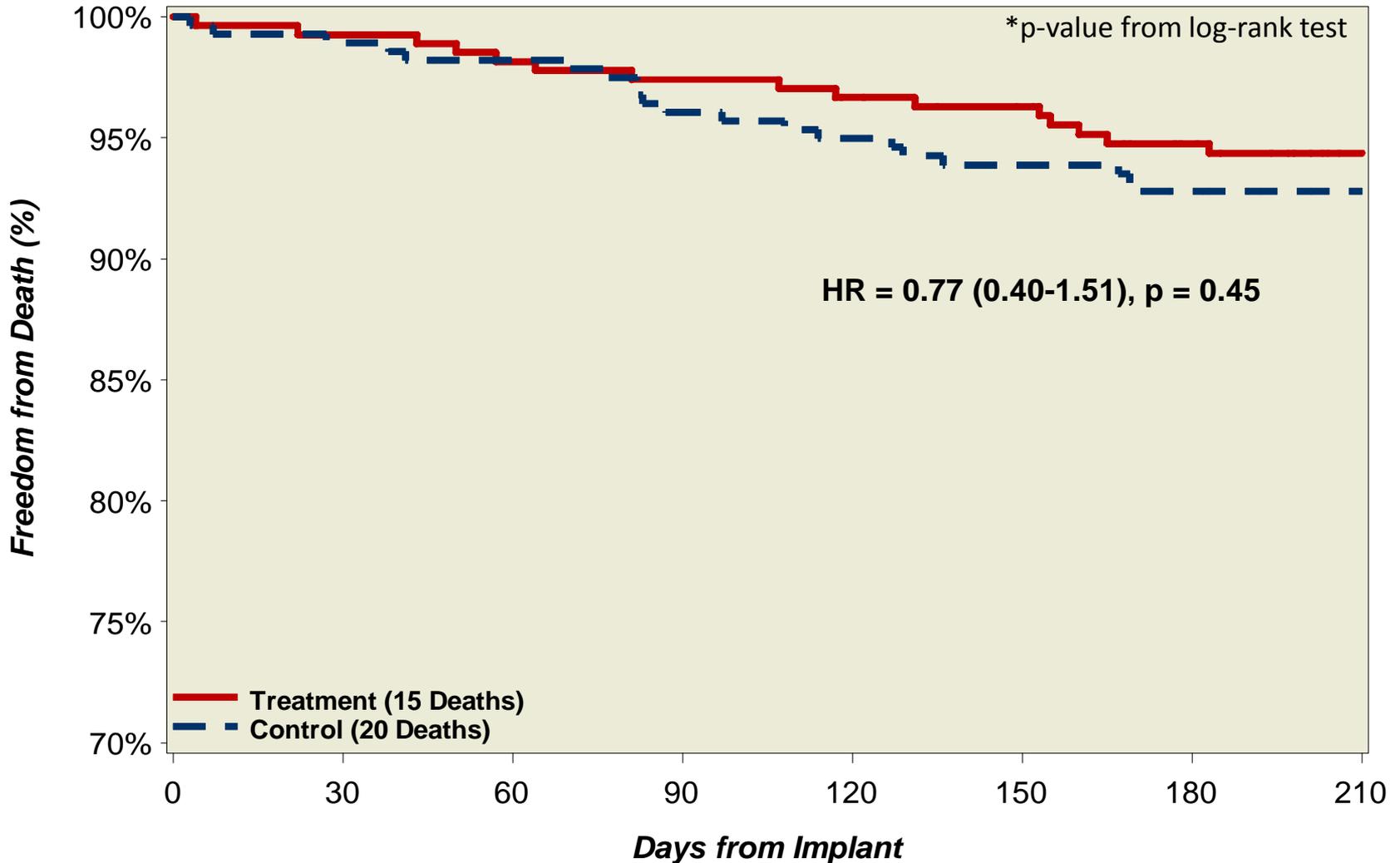
No. at Risk								
Treatment	270	268	265	262	258	254	244	230
Control	280	276	273	267	264	258	252	242

Freedom from HF Hospitalization or Death
Up to 6 Month Follow-up

*p-value from log-rank test

HR = 0.69 (0.50-0.95), p = 0.024

Treatment (63 Subjects with at least 1 HF Hospitalization or Death)
Control (91 Subjects with at least 1 HF Hospitalization or Death)

Days from Implant
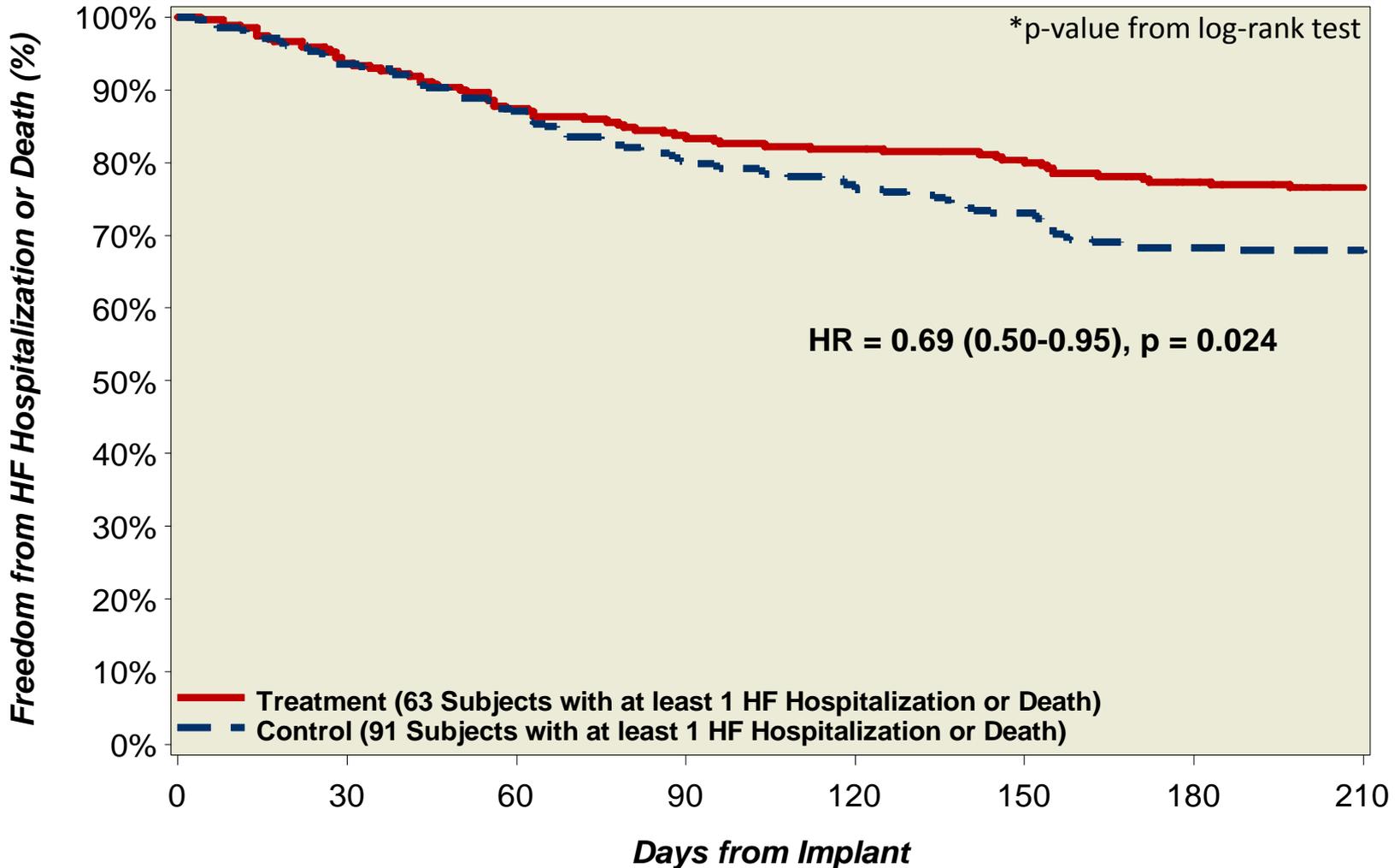
No. at Risk								
Treatment	270	253	236	225	221	213	201	186
Control	280	261	242	223	212	202	186	177

Heart Failure Medication Changes
PA Pressure versus Non-Pressure Based
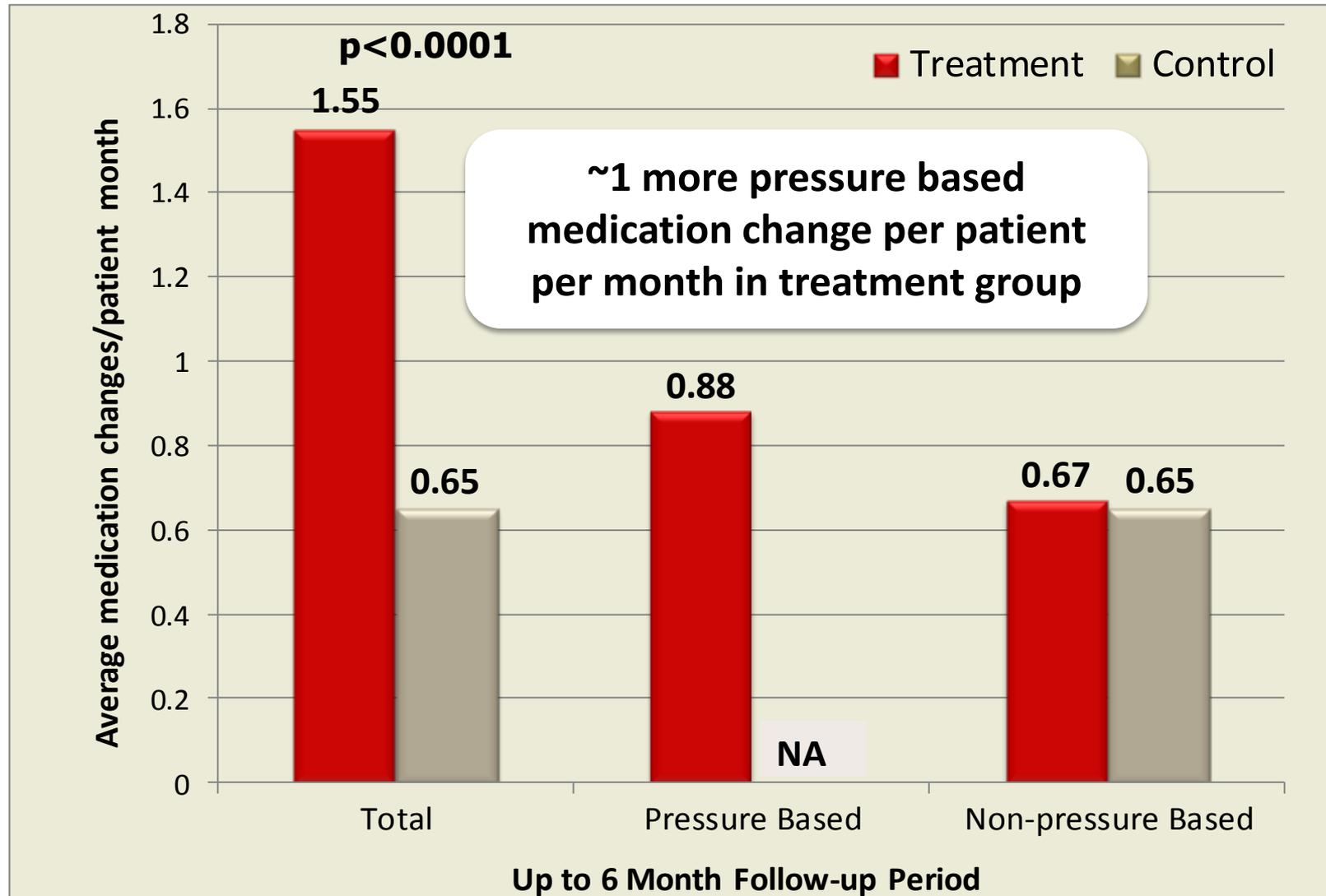
p value from Wilcoxon rank sum test

Balanced Standard of Care Interventions

|	Treatment (270)	Control (280)
	# Medication Changes	
Non Pressure Based HF Medication Changes	**1064**	**1061**
	# Subjects	
Outpatient IV Diuretics	23 (8.5%)	26 (9.3%)
Dietary Counseling	27 (10.0%)	23 (8.2%)
Sleep Apnea Treatment	35 (13.0%)	44 (15.7%)
Pulmonary Vasodilators e.g. Sildenafil	6 (2.2%)	6 (2.1%)
D/C of Contraindicated Medications (NSAIDs & TZDs)	8 (3.0%)	6 (2.1%)

Hunt SA, Abraham WT, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult J Am Coll Cardiol. 2005 Sep 20;46(6):e1-82.

Hunt, SA, Abraham WT, et al. AHA 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. J Am Coll Cardiol. 2009, 53 (15), e1-e90.

*Data not yet reviewed by FDA.

Medication Adjustments Based on PA Pressure Changes

	Patients (270)	Meds (1404)
PA Pressure Increase Leading to Med Adjustments	**204 (75.6%)**	**1262 (89.9%)**
ACE/ARB	62 (23.0%)	118 (9.4%)
Aldosterone Antagonist	23 (8.5%)	27 (2.1%)
Beta-blocker	47 (17.4%)	69 (5.5%)
Diuretic-Loop	**155 (57.4%)**	**629 (49.8%)**
Diuretic-Thiazide	**73 (27.0%)**	**212 (16.8%)**
Hydralazine	31 (11.5%)	51 (4.0%)
Nitrate	67 (24.8%)	108 (8.6%)
Other	24 (8.9%)	48 (3.8%)
PA Pressure Decrease Leading to Med Adjustments	**58 (21.5%)**	**142 (10.1%)**
ACE/ARB	5 (1.9%)	8 (5.6%)
Aldosterone Antagonist	1 (0.4%)	1 (0.7%)
Beta-blocker	7 (2.6%)	10 (7.0%)
Diuretic-Loop	**46 (17.0%)**	**107 (75.4%)**
Diuretic-Thiazide	**5 (1.9%)**	**5 (3.5%)**
Hydralazine	3 (1.1%)	3 (2.1%)
Nitrate	4 (1.5%)	7 (4.9%)
Other	1 (0.4%)	1 (0.7%)

Baseline to 6 Months
HF Medications Change in Dose

Beta-blocker -Carvedilol equivalent, ACE/ARB- Enalapril equivalent, Diuretic -Furosemide equivalent
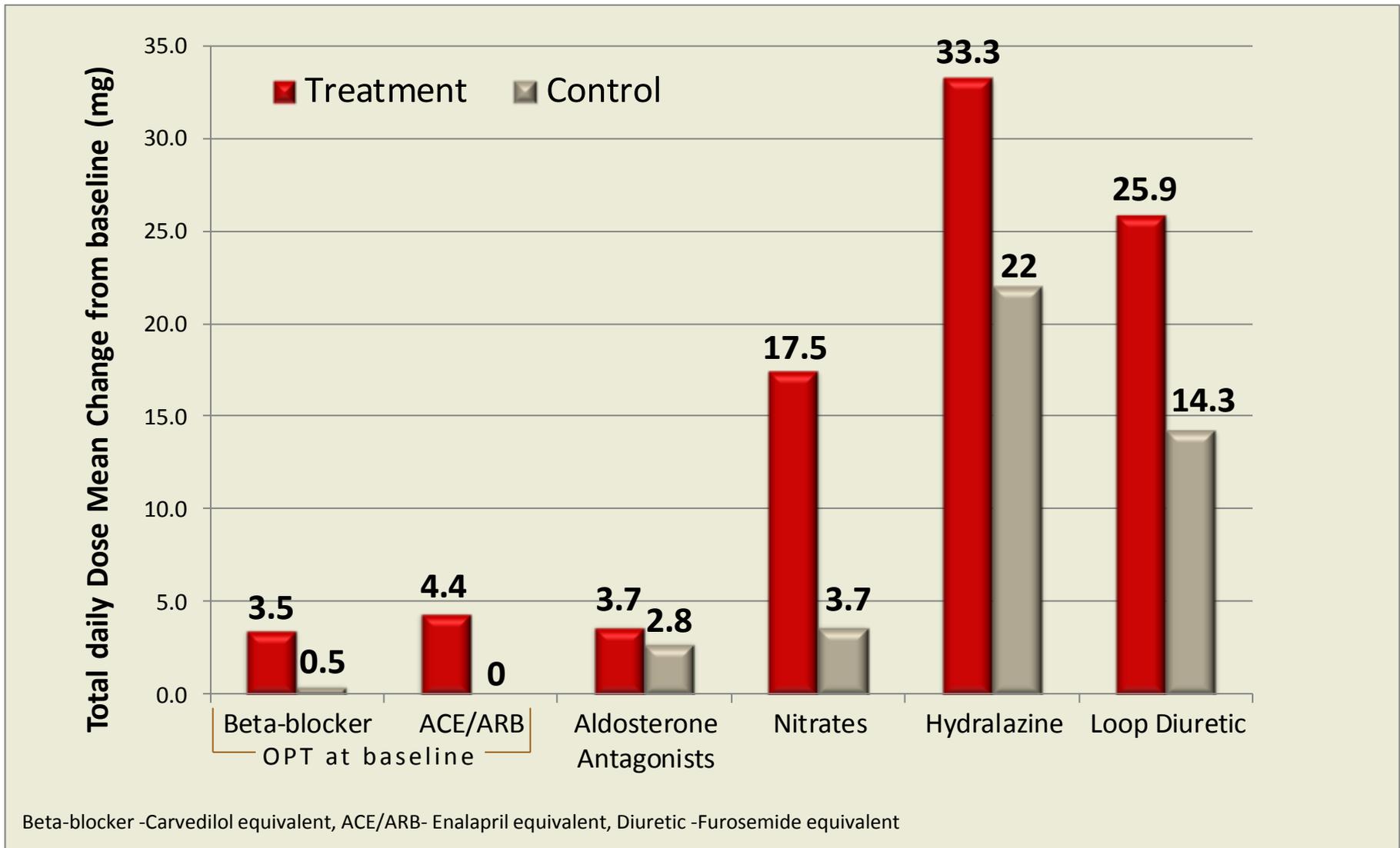
Protocol Specified Communications
Recommendations from ACC/AHA Guidelines (Appendix E)

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 warrants 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."*

Appendix E and 2005 ACC/AHA Guidelines
  Increase Diuretics, Change Diuretics
  <u>Appendix E- pg. 3:</u>
  Hyper-volemic Treatment Recommendations

  • *Add or increase diuretic (and appropriate electrolyte replacement)*

  a. ***Increase or add loop diuretic***

  b. *Change to another loop diuretic*

  c. *Add thiazide diuretic (with caution)*

  d. *IV doses of loop diuretic*

  e. *Serum electrolyte evaluation with change in baseline medication*

  f. *Re-assess pulmonary artery pressure utilizing the HF Pressure Measurement System at least 2 – 3 days per week until optivolemic*

PA Pressure Medication Changes Secondary to Email

	First 6 Months	After 6 Months to Unblinding	After Unblinding
	N= 270 Treatment Patients 6 Months	N= 244 Treatment Patients 9 Months	N=383 All Patients 17 Months
CardioMEMS Follow-up Emails	**391**	**360**	**0**
Inquiry Emails	198	229	na
Recommendation Emails	193	131	na
Emails/patient month	**0.25**	**0.14**	**na**
PA pressure med changes/patient month	0.88	0.28	0.23
PA Pressure Med Changes/patient month associated with CM Inquiry Email	0.04 (4.4%)	0.01 (3.2%)	na
PA Pressure Med Changes/patient month associated with CM Recommendation Email	0.04 (5.5%)	0.02 (3.5%)	na
PA Pressure Med Changes/patient month made independently by Investigator	**0.81 (90.0%)**	**0.25 (93.4%)**	**0.23 (100.0%)**

*Data not yet reviewed by FDA.

Medication Changes

- 1404 medication changes due to pressures
  - 953/1404 (68%) were diuretics

- 61 medication changes made within 72 hours of recommendation email
  - 41/61 (67%) were diuretics

Principal Findings: CHAMPION Trial

Hypothesis

HF Management Based on Pulmonary Artery Pressure
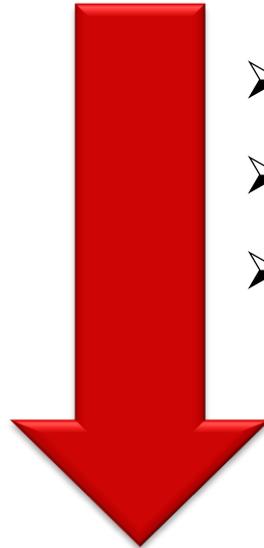
➤ PAP Based Med Changes (p<0.0001)

➤ PA Pressure Reduction (p=0.0077)

➤ QOL Improvement (p=0.0236)

28% Heart Failure Hospitalization Reduction
(p=0.0002)

p values for Treatment vs Control Group

Full Study Duration Analysis

- Patients remained blinded and in their original assigned study groups until after the 550th patient reached 6 month follow-up

- Resulted in an average follow-up of 15±7 months (maximum 30 months)

- Safety, efficacy, secondary and supplementary analyses were repeated over full study duration

- These analyses included but were not limited to:
  - Safety Data
  - Cumulative HF Hospitalizations
  - Non HF Hospitalizations
  - Survival

Supplementary Analysis
Safety from 6 months to End of Study

Safety endpoints based on 498 patients after 6 months

1. **Freedom from Device/System Related Complications (DSRC)**

   – **498 (100.0%,** lower 95% CL = **99.3%)**

2. **Freedom from Pressure Sensor Failures**

   – **498 (100.0%,** lower 95% CL = **99.3%)**

Supplementary Efficacy Endpoint Met
Full Duration

	Treatment (n=270)	Control (n=280)	Relative Risk Reduction	p-value
# HF Hospitalizations (Annualized Rate)	158 (0.46)	254 (0.73)	**37%**	**<0.0001**

p-value from negative binomial regression
NNT = Number Needed to Treat

- Number needed to treat = 4

No Increase in Non-Heart Failure Hospitalizations

	Treatment Hospitalizations	Control Hospitalizations	Difference	p-value
6 Months				
All Cause Hospitalizations	232	263	31	0.41
HF Hospitalizations	84	120	36	**0.0002**
Non-HF Hospitalizations	**148**	**143**	**5**	0.58
Full Study Duration				
All Cause Hospitalizations	496	597	101	0.33
HF Hospitalizations	158	254	96	**<0.0001**
Non-HF Hospitalizations	**338**	**343**	**5**	0.84

p-value from negative binomial regression

Freedom from Death
Over Full Study Duration Until Patient Unblinding

*p-value from log-rank test

HR = 0.81 (0.56-1.16), p = 0.25

Treatment (51 Deaths)
Control (65 Deaths)

Days from Implant
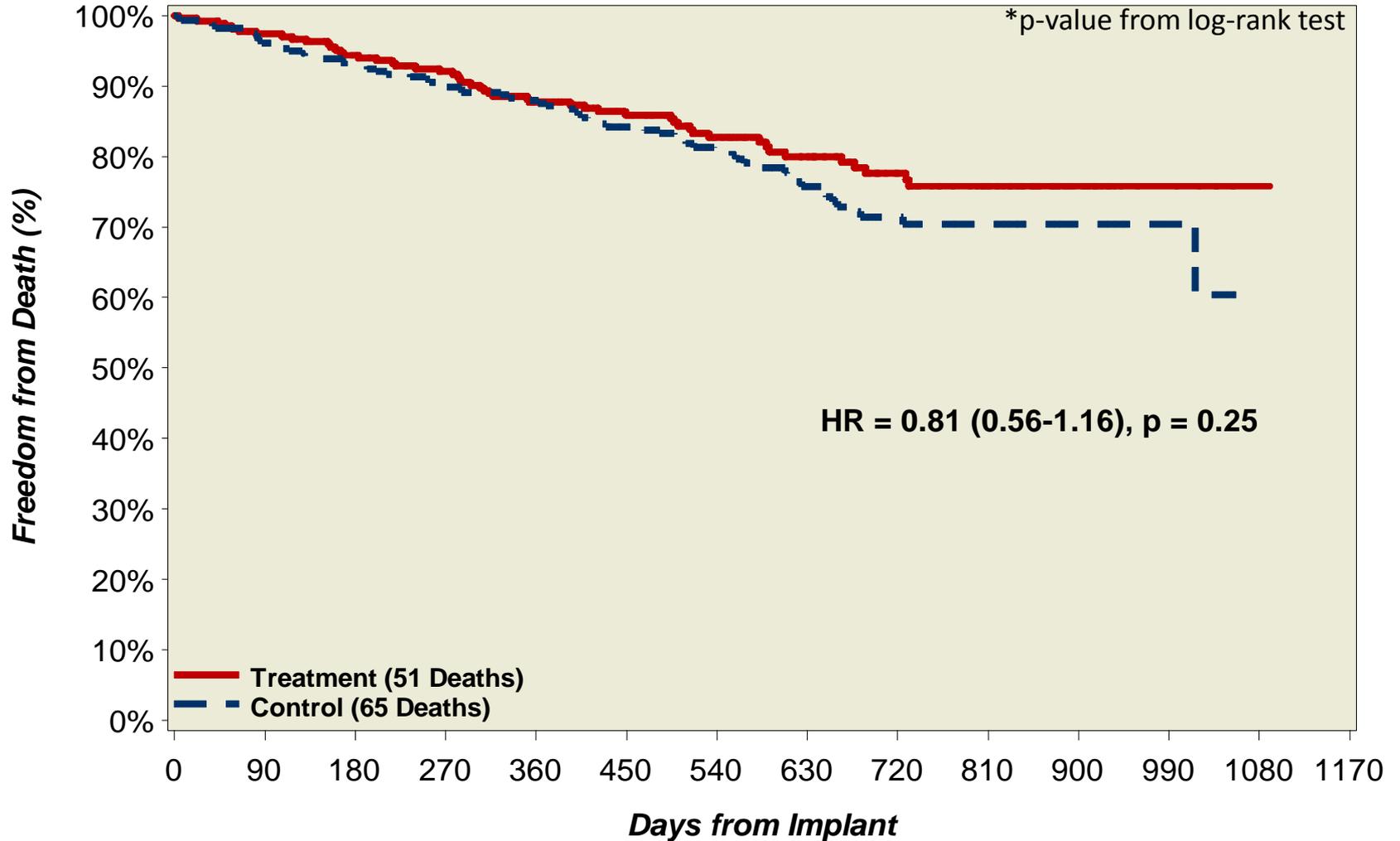
No. at Risk													
Treatment	270	262	246	236	212	180	142	113	86	62	23	5	1	0
Control	280	267	254	241	223	186	146	108	73	48	20	7	0	0

Freedom from HF Hospitalization or Death
Over Full Study Duration

*p-value from log-rank test

HR = 0.73 (0.57-0.94), p = 0.015

Treatment (111 Subjects with at least 1 HF Hospitalization or Death)
Control (139 Subjects with at least 1 HF Hospitalization or Death)

Freedom from HF Hospitalization or Death (%)

Days from Implant
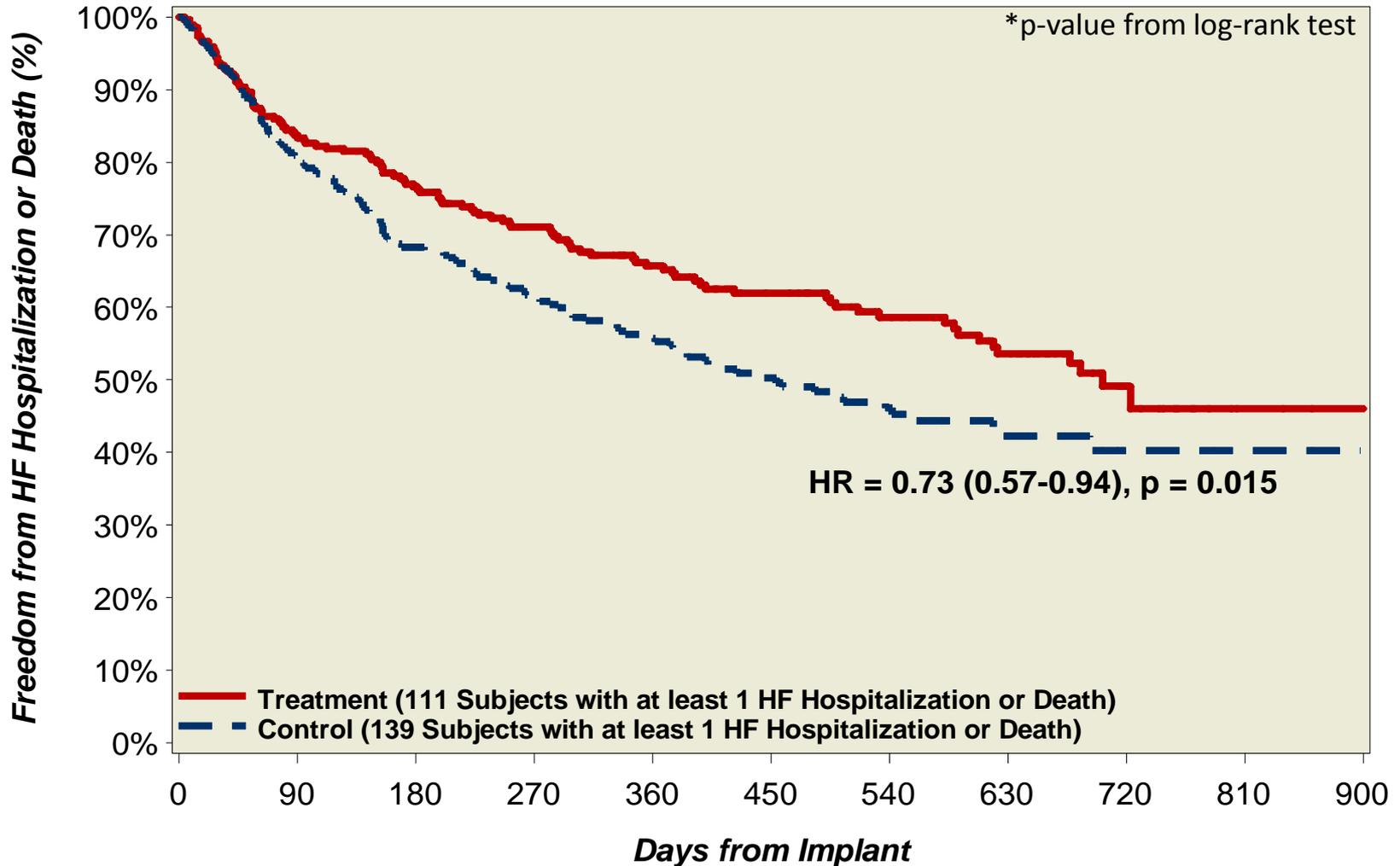
| No. at Risk	0	90	180	270	360	450	540	630	720	810	900
Treatment	270	225	201	168	130	104	83	62	17	4	1
Control	280	223	186	145	112	79	56	38	13	6	0

Outcomes Following Unblinding

Investigator reported events.

*Data not yet reviewed by FDA.
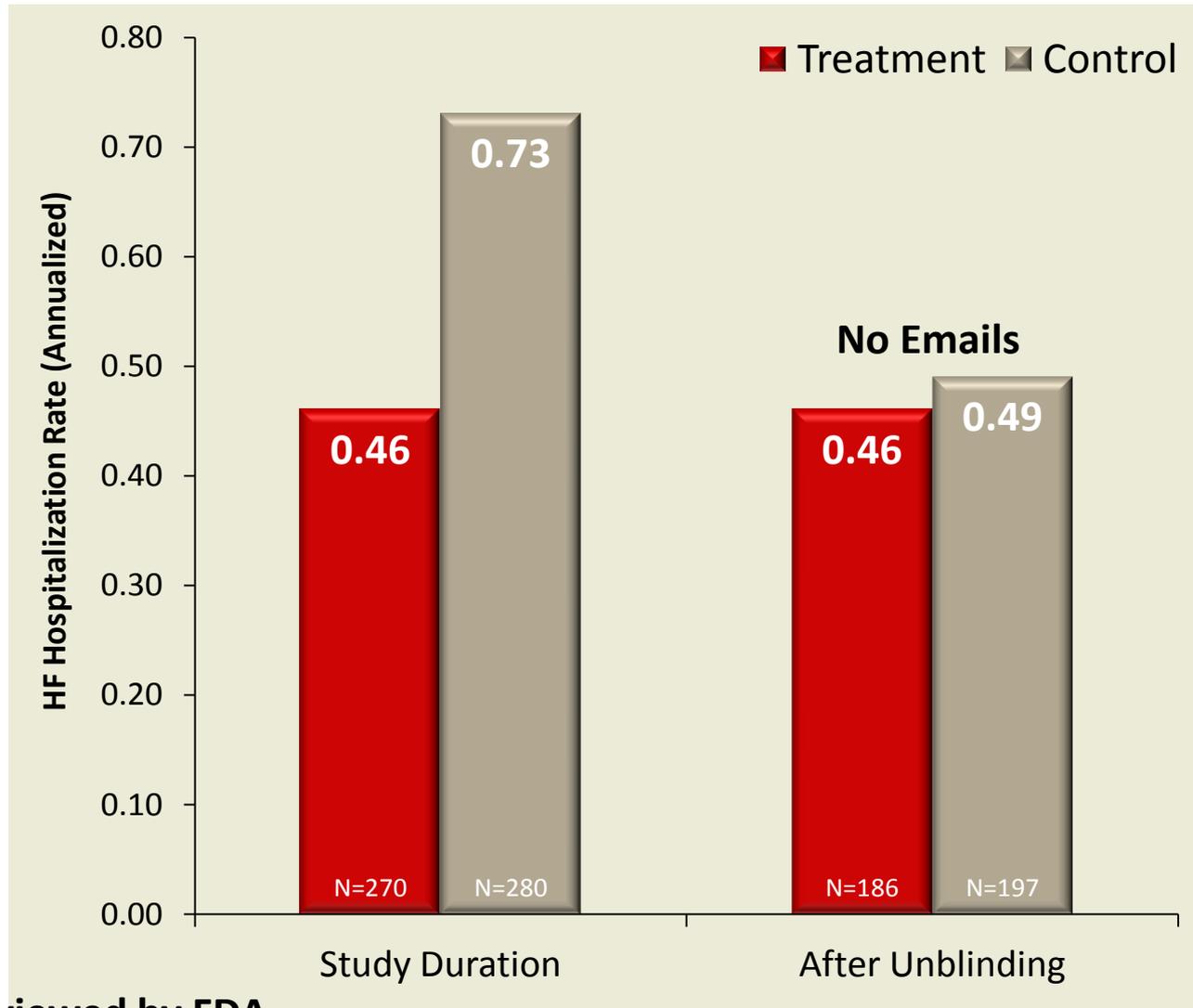
FDA Trial Conduct Concerns

- *"Made specific treatment recommendations for Treatment group only"*
  - Uniform high level standard of care for both groups
  - Pressure management for Treatment group:
    - Essential part of implementing this new treatment paradigm
    - Appendix E: Would differ from previous studies in making specific recommendations
    - Appendix E: Consultation with PIs was recommended

- *"Level of interaction between sponsor and clinical investigators inconsistent with FDA's expectations"*
  - Appendix E of the Protocol was designed and revised with FDA input from 2006-2007

- *"FDA concerned these actions may bias results"*
  - Integral part of protocol and testing of hypothesis

- *"Measures…would not be duplicated in post-market setting"*
  - Education and support designed for post market setting
  - Committed to post marketing support
  - Many approved devices require higher levels of support

CHAMPION Trial Achieved
All Primary Safety and Efficacy Endpoints

✓ **Primary Safety Endpoints**

- 98.6% Freedom from Device/System Related Complications, lower CL **97.3%** < OPC of 80%

- 100% Freedom from Sensor Failures, lower CL **99.3%** < OPC of 90%

✓ **Primary Efficacy Endpoint**

- 28% Reduction in Rate of HF hospitalizations (p=0.0002)

CHAMPION Trial Achieved
All Secondary Efficacy Endpoints

✓ **Secondary Efficacy Endpoints**

- Reduction in Pulmonary Artery Pressure (p=0.0077)

- Reduction in Percent of Patients Hospitalized (p=0.0292)

- Increase in Days Alive Outside of Hospital (p=0.0280)

- Improvement in Quality of Life (p=0.0236)

CHAMPION Trial Achieved
Primary Safety and Efficacy Endpoints Over Study Duration

✓ **Safety and efficacy were maintained over full study duration**

- No additional device/system related complications or sensor failures after 6 months (p<0.0001)

- 37% reduction in rate of HF hospitalizations (p<0.0001)

Conclusion

The CardioMEMS *Champion* HF Monitoring System offers a significant improvement in management for patients with NYHA Class III HF, leading to fewer HF hospitalizations and better quality of life.

General Statistical Considerations

Richard Holcomb, PhD

Independent Statistician
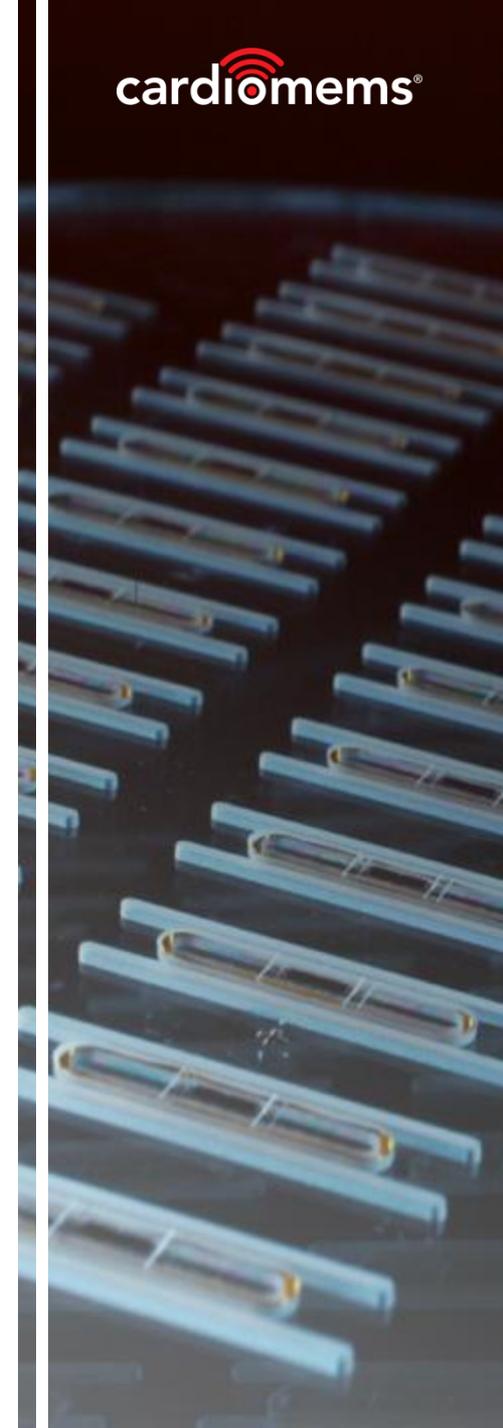
Comments on FDA Statistician's Analyses

FDA statistician:

- <u>Confirmed</u> that primary and secondary endpoints were met according to pre-specified analyses in the FDA approved SAP

- Performed exploratory analyses using other event counting models
  - Most post-hoc models support the study findings
  - Over full study duration, all models demonstrate significance

- Provided tipping point analysis
  - As expected, reducing treatment effect eventually leads to non-significant results, i.e., RRR 28% reduced to 16%
  - Robustness demonstrated by:
    - p-value of primary efficacy results ($p = 0.0002$)
    - Consistency of results of all endpoints and time intervals

Bias or Planned Intervention?

You may hear that "the 2 study arms were treated differently."
- Treatment interventions in 2 study arms differed by design
- Sponsor took steps to ensure protocol was followed

You may hear that "only subjects were blinded in the study."
- Yes, this was a single-blind study; subjects were blinded
- All patients received device and scripted matched calls
- Investigators could not be blinded since their role was to use sensor information to manage PA pressures
- Independent CEC evaluation of the primary study endpoint was blinded

Medical Management

Ty Cowart, MBA/MPA, JD, LLM

Vice President, Regulatory Affairs
CardioMEMS

SOP-000105: CHAMPION Subject Qualifying and Medical Management

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	Standard Operating Procedure Number	**SOP-000105**
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Recommended Structure For Nurse Email Communications

Attachment E – Email example to discuss Medical Management of Treated patients

In our review of patients with similar challenges, the following therapeutic strategies were recommended by the CHAMPION Trial National Principal Investigators, Dr. William Abraham and Dr. Philip Adamson.

1. *List treatment and reason why it is being recommended*
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Post Approval Study and Training

Jay S. Yadav, MD, FACC
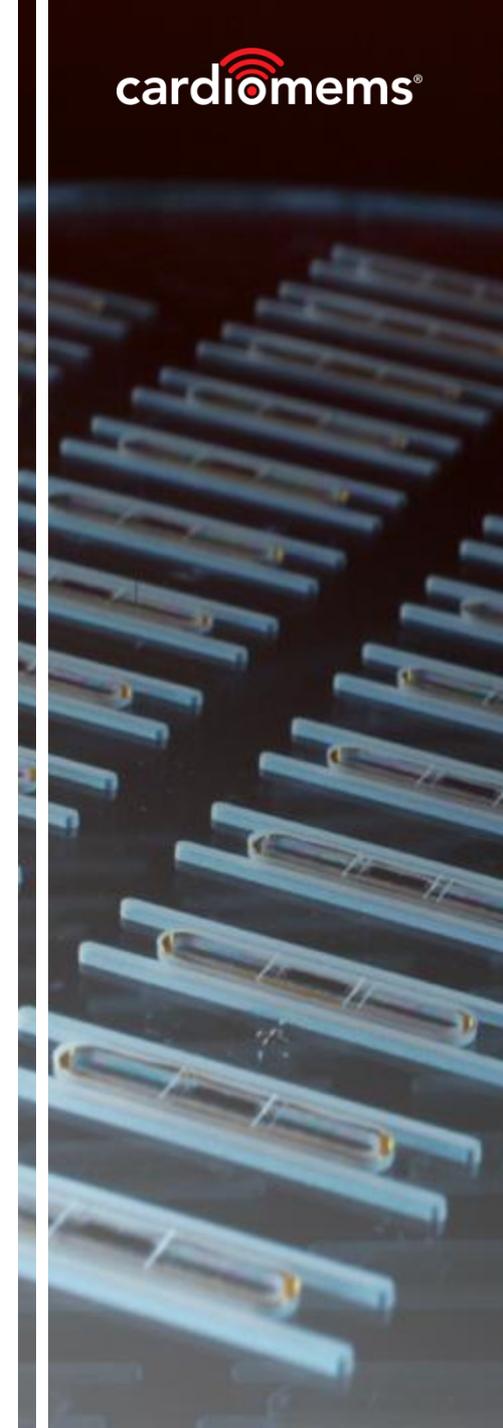
Post Approval Study

- CHAMPION demonstrated acceptable level of safety and effectiveness

- Commitment to gathering additional data in the commercial setting

- Tentative designs under consideration

  - Proposed design in Briefing book

  - HF Registry with governing body in conjunction with professional societies (ACC, AHA, HFSA, HRS, SCAI)

Methods and Tools for Training

IN PERSON

- **Cath. Lab**
  - Training on implant and calibration through certification and beyond with or w/o preceptor

- **Post Implant**
  - Nurse training on patient instructions for use

- **Clinic**
  - Training on use of CHAMPION website and data interpretation and to ensure proficiency

MULTIMEDIA

- **Animations**
  - Physician/Nurse Implant + Data screen
  - Patient use of home electronics

- **Videos**
  - Patient Testimonial
  - Nurse Testimonial

- **PowerPoint**
  - PPT and Publication Library

- **Newsletter**

INTERACTIVE

- **Webinars**
  - Cath. Lab Implant Training
  - NP/HF Nurse Data Mgmt. Training

- **Company Website Material**
  - Guidelines
  - Case Studies
  - Interactive Self Assessment

Training Plan for Sites

Overview of pathophysiology of HF → **Traditional HF management strategies**

Implementation of Guidelines for Managing HF Using PA Pressures

APPENDIX E: MANAGEMENT OF HEMODYNAMIC PARAMETERS

The hypothesis of the CHAMPION trial is that heart failure management using pulmonary artery pressures reduces the rate of heart failure hospitalizations. The unique nature of the implanted device allows intermittent assessment of pulmonary artery systolic, diastolic and mean pulmonary artery pressures. The key to adequate testing of this hypothesis is that pressures should be used for the basis of clinical decision making in addition to symptoms, weights or physical examination (traditional markers of volume).

Guidelines for managing heart failure using pulmonary artery pressures

The CHAMPION trial will differ from previous hemodynamic monitoring studies in that specific recommendations will be made to utilize pressures in heart failure management including use of diuretics and vasodilators.

Pulmonary Artery Pressure Goals:

PA Systolic	15 - 35 mmHg
PA Diastolic	8 - 20 mmHg
Mean PA pressure	10 - 25 mmHg

Case Studies

Commercial Setting

Patient

Care Team

Treatment decisions

Website

Takes pressure readings

Readings

Login

Alerts

Reviews readings on Web site

Guideline reminders

cardiomems®
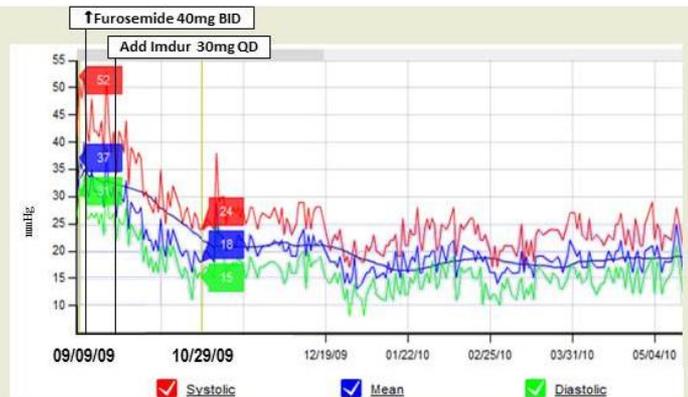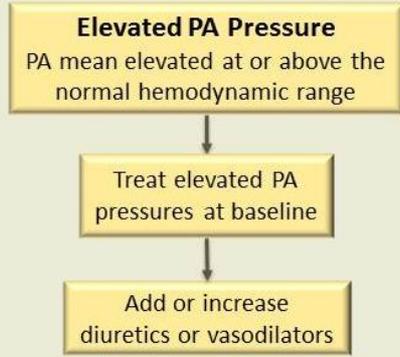
Automated analysis with nursing review

Patient Centered Heart Failure Management

- Heart failure hospitalizations remain a significant burden

- Technology:
  - Ease of implant and use
  - Long term accuracy and reliability in ambulatory setting

- Pressure based management strategy:
  - Sets a new standard for safety
  - Reduces heart failure hospitalizations
  - Improves quality of life

CHAMPION Trial

✓ Met all Primary Safety and Efficacy Endpoints

✓ Met all 4 Secondary Efficacy Endpoints

CardioMEMS *Champion*™ Heart Failure Monitoring System

Supportive Slides
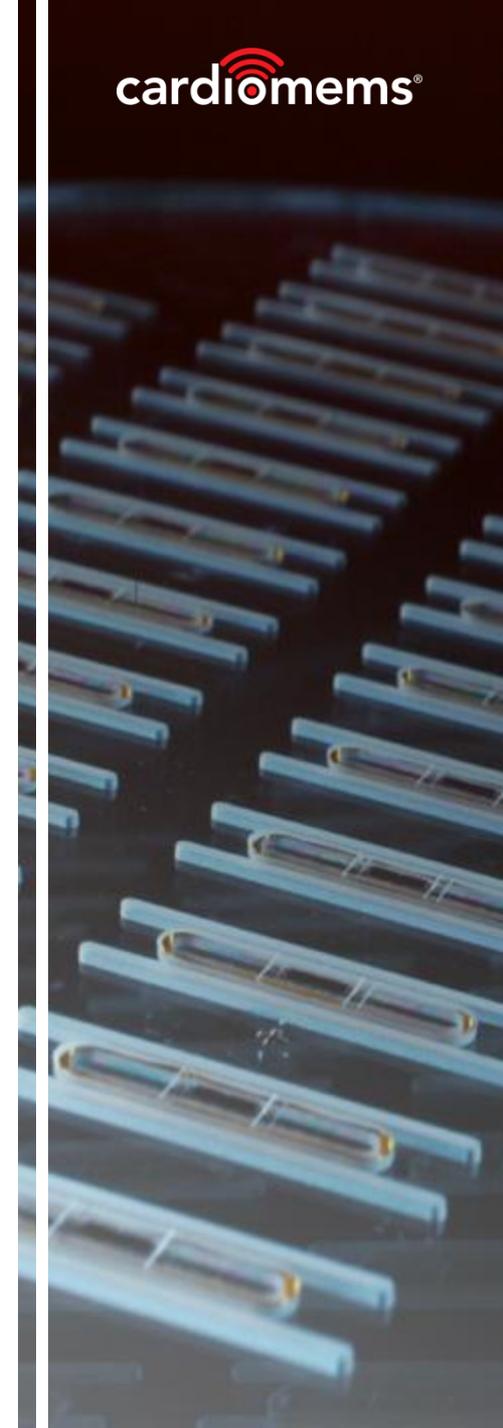
Phone Call Script

A matching phone contact will be generated to a CONTROL group subject when a contact is made to a TREATMENT group subject.

The script for both contacts will be identical with the exception of the medication adjustment made to the TREATMENT group subject.

Script
TREATMENT group:
"Hello, (*insert subject's name*), this is *(insert clinician's or coordinator's name)* from *(insert institution).* Thank you for taking your HF pressure measurements. At this time, we would like you to (insert treatment plan, i.e., increase lasix to 40 mg bid, etc.). Please continue to take your daily HF pressure measurements.
Thank you."

CONTROL group:
"Hello, *(insert subject's name),* this *is (insert clinician's or coordinator's name)* from *(insert institution).* Thank you for taking your HF pressure measurements. At this time, we are not making any changes to your medications. Please continue to take your daily HF pressure measurements.
Thank you."

When a TREATMENT group subject is contacted, the site personnel will randomly select a subject from the CONTROL group and will contact that subject as soon as reasonably possible.

Quality of Life MLHFQ Total Score
Subjects with/without HF Hospitalization
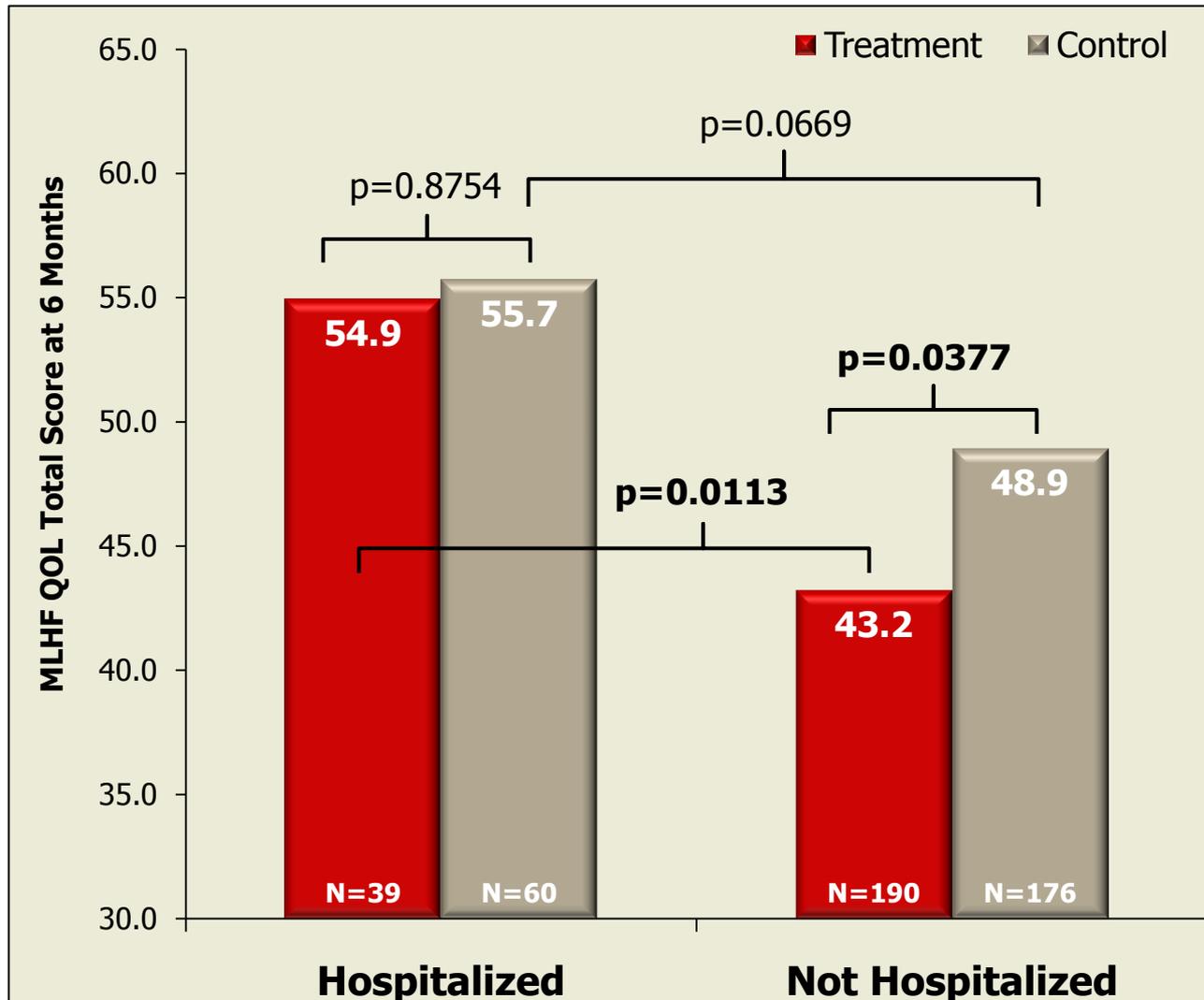
P-value testing Treatment vs. Control obtained from GLM

Lower score = better QOL

Eliminating Bias Related to Patient Contact

- Standard scripts used for all patient contact

- After each contact to a Treatment patient, a call was made to a randomly selected Control patient

- This matching contact helped to maintain the single blind status of the trial

	Subject Contacts		
Analysis	TREATMENT (270)	CONTROL (280)	p-value
Calls Per Patient Per Site within 6 Months	3.0	2.5	0.4902

p-values obtained from Wilcoxon signed-rank test comparing mean calls between treatment and control groups based on 53 sites with at least 1 treatment patient and 1 control patient simultaneously.

Clinic Visits between Randomization Groups

- Follow-up study visits for both groups were at 1, 3, 6 and every 6 months for three years
- Study visits were balanced between groups

				Study Visits			
Site	Baseline	Month 1	Month 3	Month 6 (Primary)	Month 12	Month 18	Month 24
Total	100.0%	96.9%	96.0%	96.8%	95.8%	92.1%	96.8%
Treatment	100.0%	97.8%	97.3%	97.1%	94.2%	94.2%	94.4%
Control	100.0%	96.0%	94.7%	96.5%	97.3%	90.2%	100.0%
P-value	1.0000	0.3252	0.1806	0.8010	0.1912	0.3184	0.5023

- There was no difference in unscheduled clinic visits between the two groups.

	Unscheduled Clinic Visits			
	TREATMENT (270)	CONTROL (280)	ALL PATIENTS (550)	p-value
Mean±StdDev (N)	0.1±0.5 (270)	0.1±0.3 (280)	0.1±0.4 (550)	0.3659

Classification of Hospital Admissions

- Most patients were admitted through ER by non-study physicians. ER records showed little evidence of PI calling patient or ER doctors with instructions for admission

- The treatment and control groups were well balanced (17 vs. 20) in the number of patients admitted after a study visit or from clinic

- The difference in hf hospitalizations of 36 events between the treatment and control groups was predominantly driven by the difference in ER admissions (91 – 59 = 32 hospitalizations)

	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

Sub-group Analysis – Atrial Fibrillation
Rate of HF Hospitalizations

|	Treatment			Control		
	Subjects	# Hosp.	Hosp. Rate (events/ patient-6 mo.)	Subjects	# Hosp.	Hosp. Rate (events/ patient-6 mo.)
Atrial Fibrillation	120	43	0.36	135	75	0.57
No Atrial Fibrillation	150	41	0.28	145	45	0.32

AG Stratified Analysis p-value = 0.0272, HR[95% CI] = 0.730 [0.552, 0.965]

Average PA Mean Pressure Prior to Hospitalization
HF Hospitalization Compared to Non-HF Hospitalization
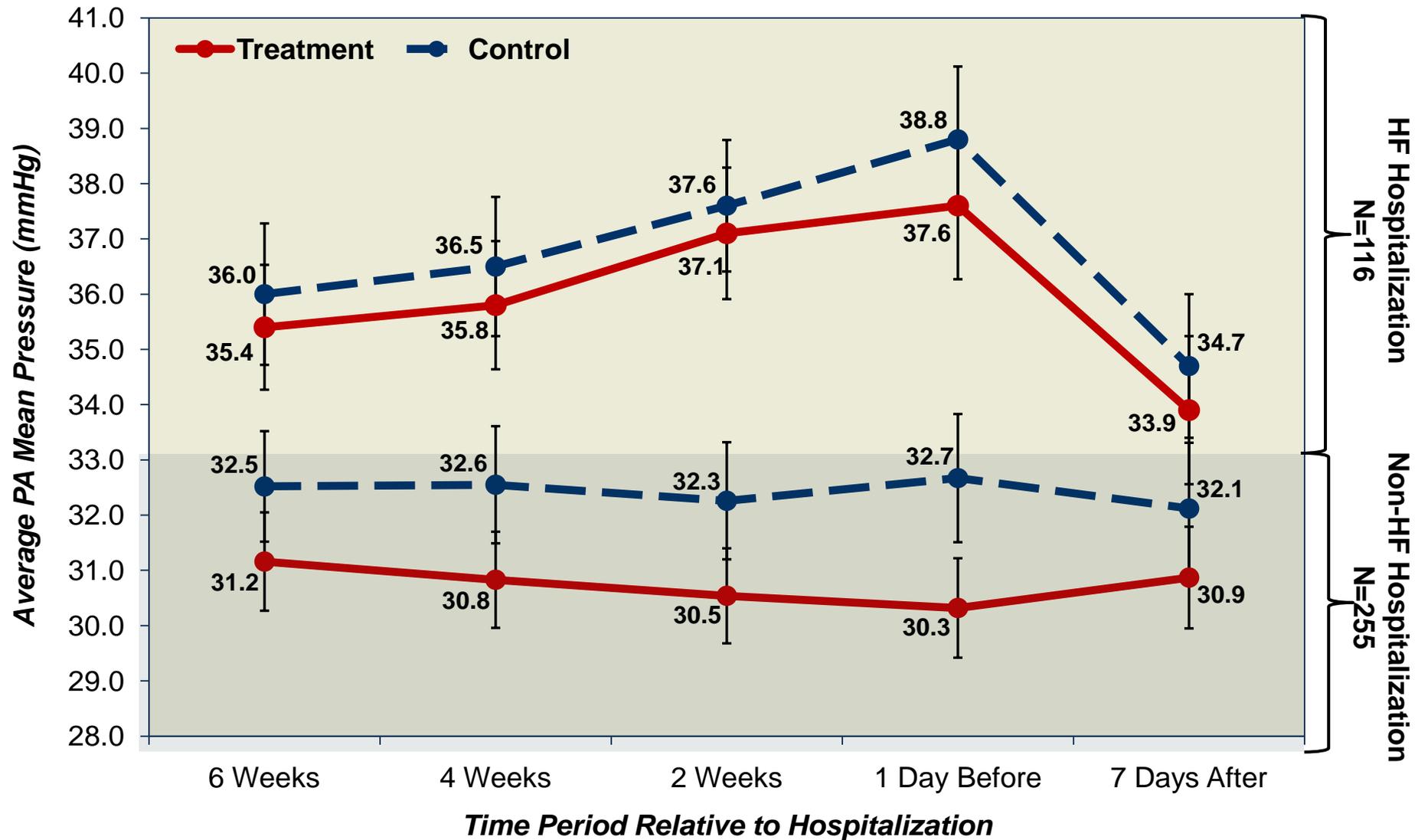
Pressure Readings → Investigator Reviews → Recommendation Emails 6 Months

44,000

12,750

193

Patient PA Readings Investigator Log Ins Recomm. Emails
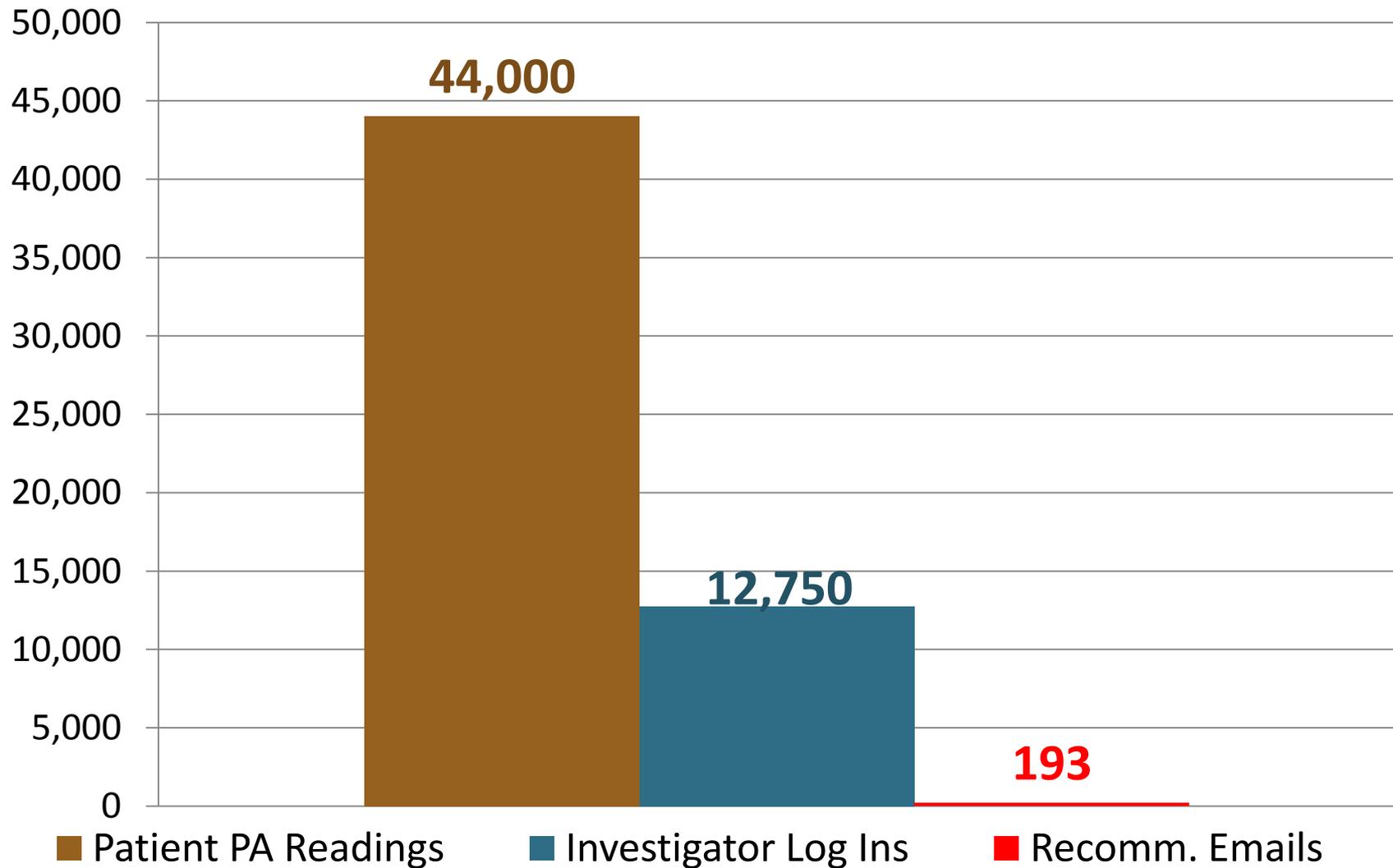
*Data not yet reviewed by FDA.

Recommendation Emails Decrease Over Time

	First 6 Months	After 6 Months to Unblinding	After Unblinding
	N= 270 Treatment Patients 6 Months	N= 244 Treatment Patients 9 Months	N=383 All Patients 17 Months
Recommendation Emails	193	131	0
Recommendation Emails/patient month	0.12	0.05	0

	First 6 Months	After 6 Months to Unblinding	After Unblinding
PA Pressure Med Changes/patient month made independently by Investigator	0.81 (90.0%)	0.25 (93.4%)	0.23 (100.0%)

*Data not yet reviewed by FDA.

Impact of Emails on Outcomes

Treatment Patients (HF Hosp. Rate)	Up to 6 Months [6 Month HF Rate]		Control
	Emails 151 (0.36)	**No Emails** 119 (0.26)	**No Emails** 280 (0.44) p=.0003

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Outcomes Following Unblinding

Investigator reported events.
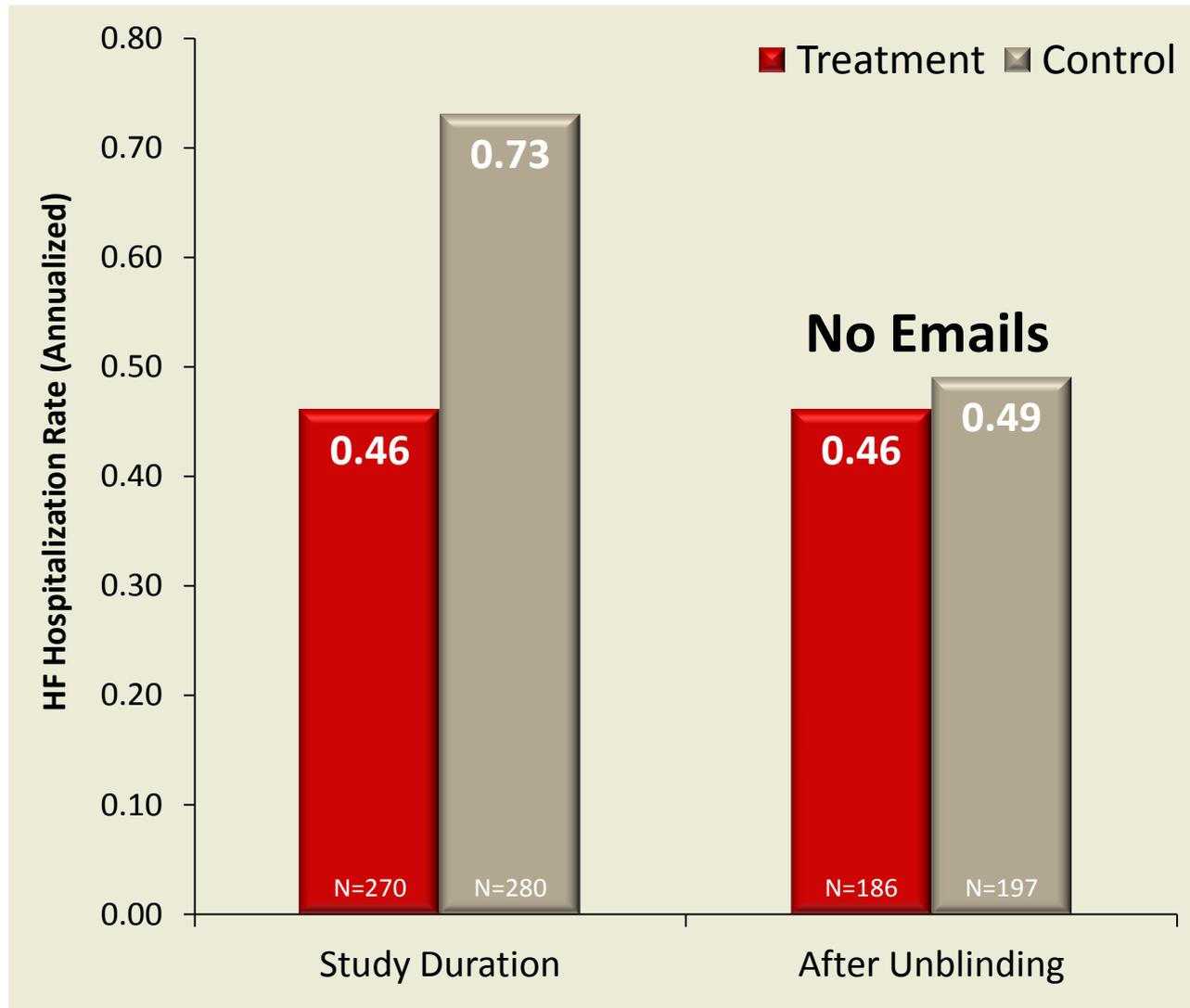
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Testing the Hypothesis

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In addition to these specific guidelines, the investigator should also incorporate the recommendations set forth in the ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult.

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Learning Curve
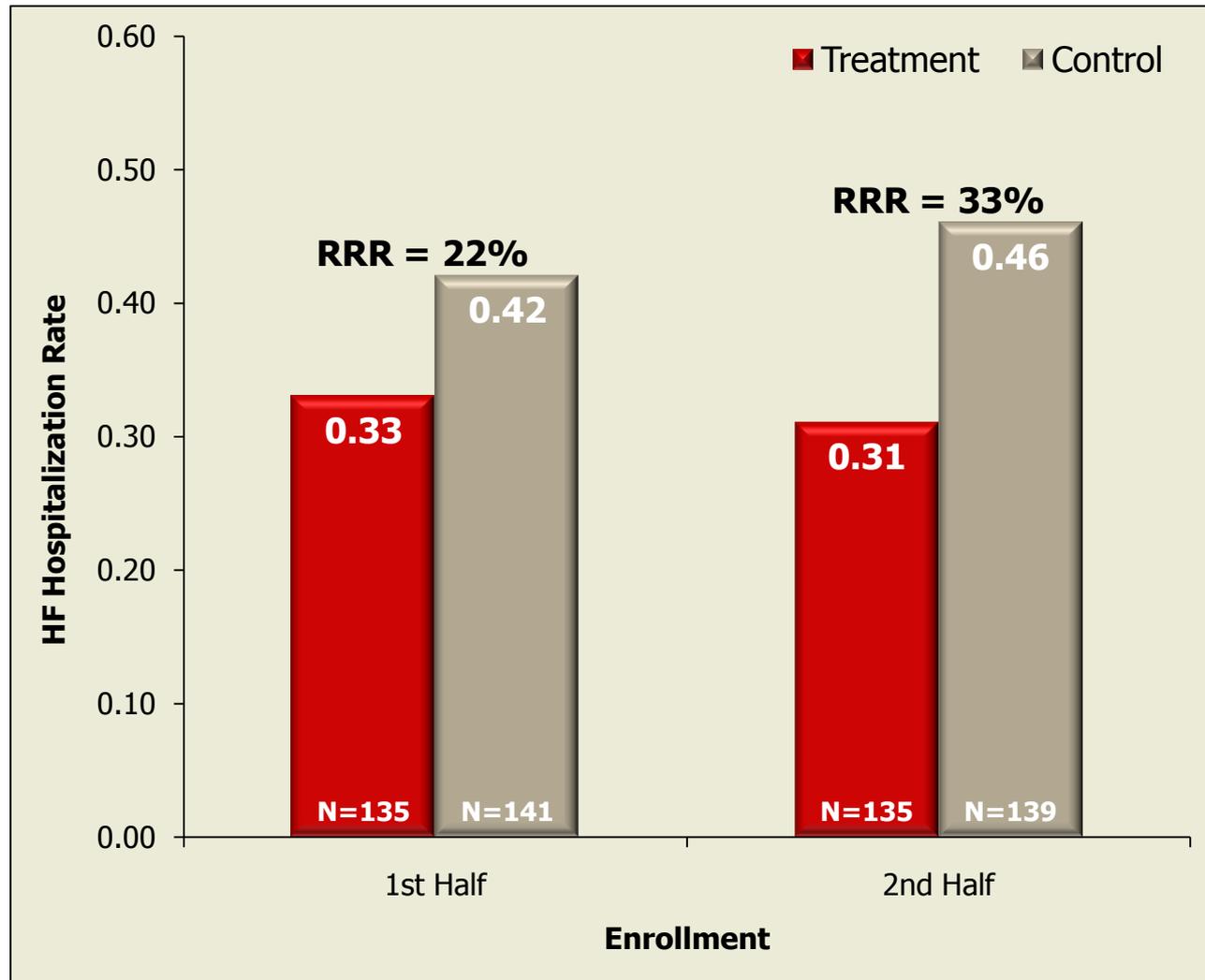
Heart Failure Medication Changes
## PA Pressure versus Non-Pressure Based
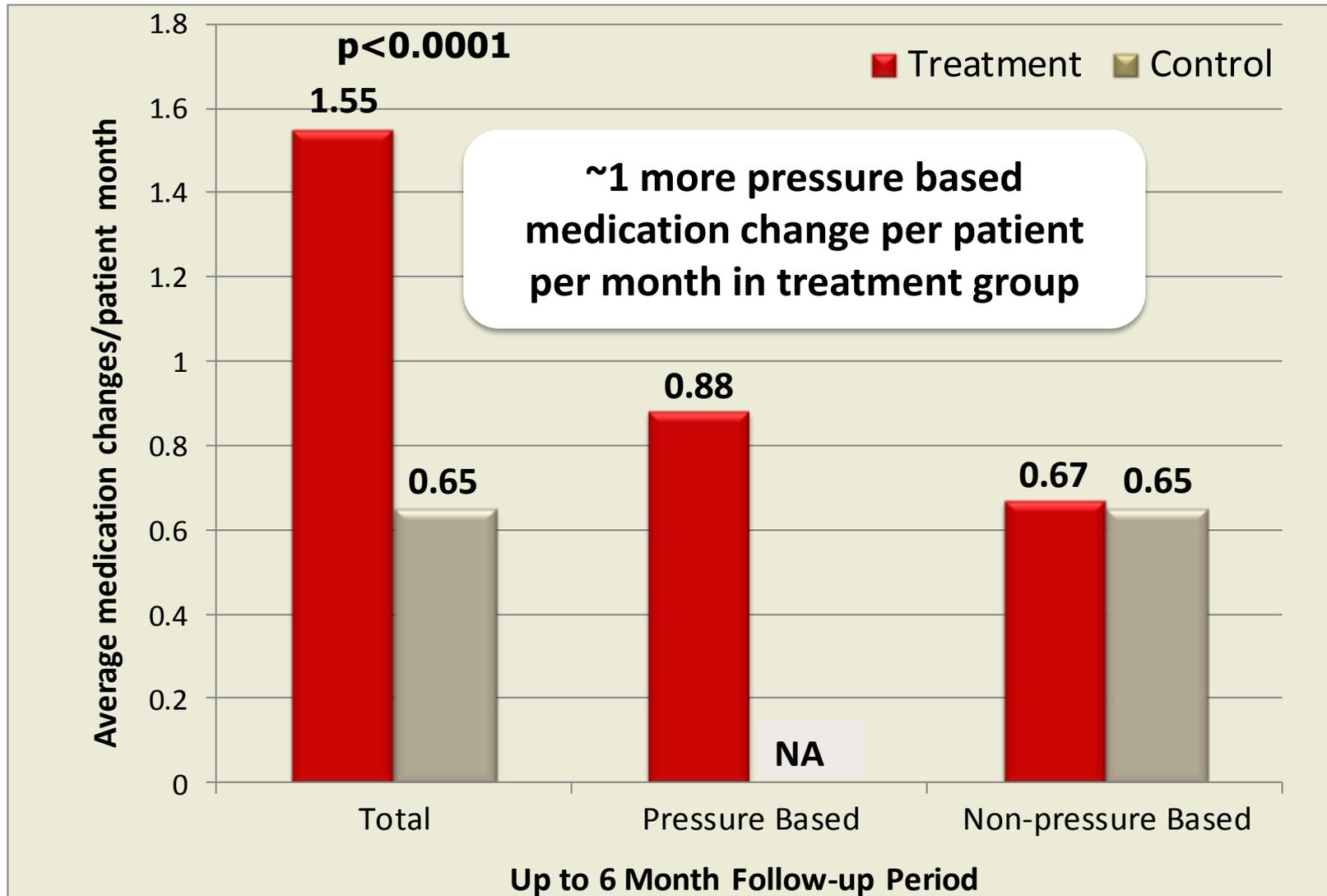
p value from Wilcoxon rank sum test

Cumulative Rate of HF Hospitalization
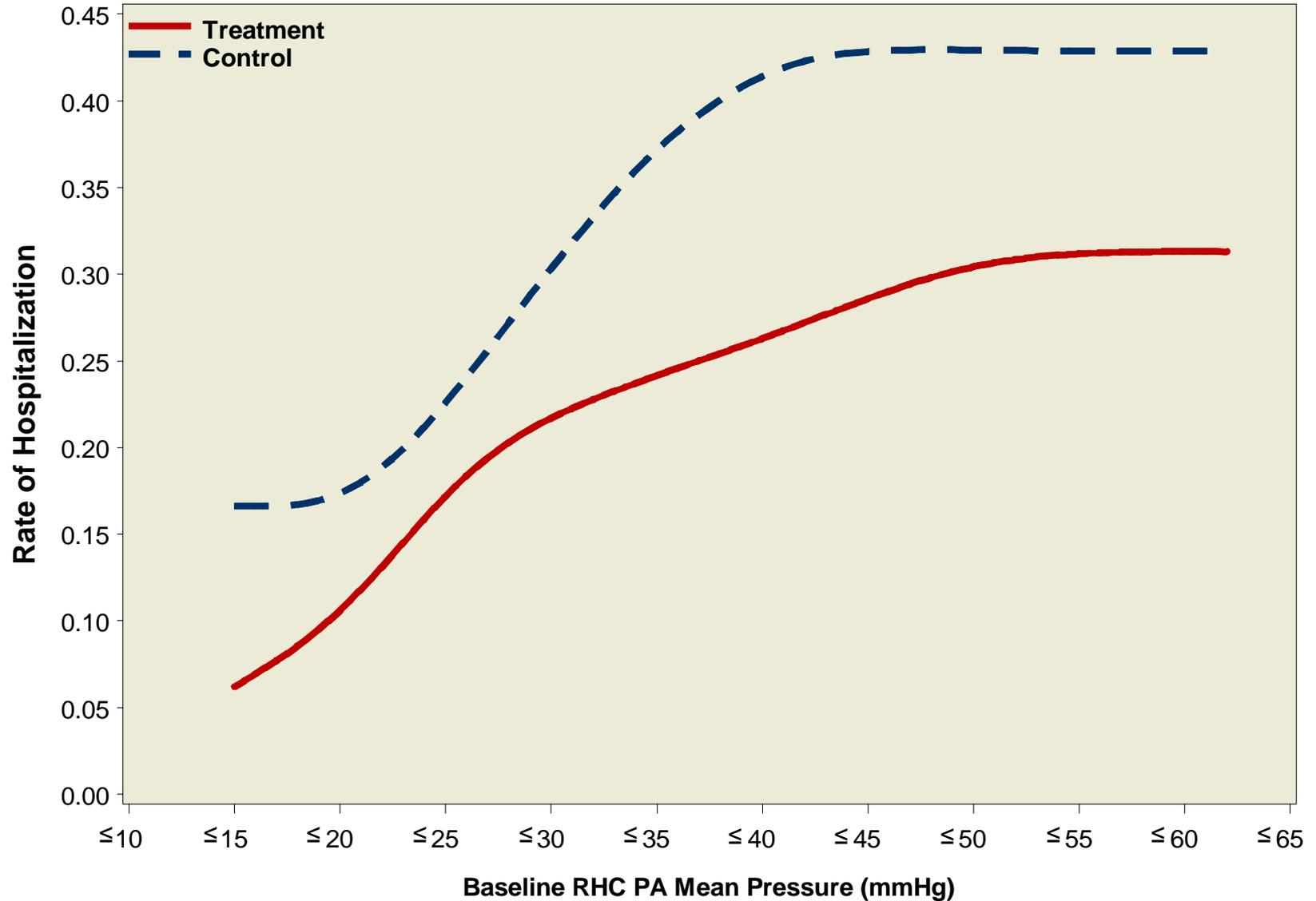
# Baseline PA Mean Pressure vs. Area Under the Curve (AUC)
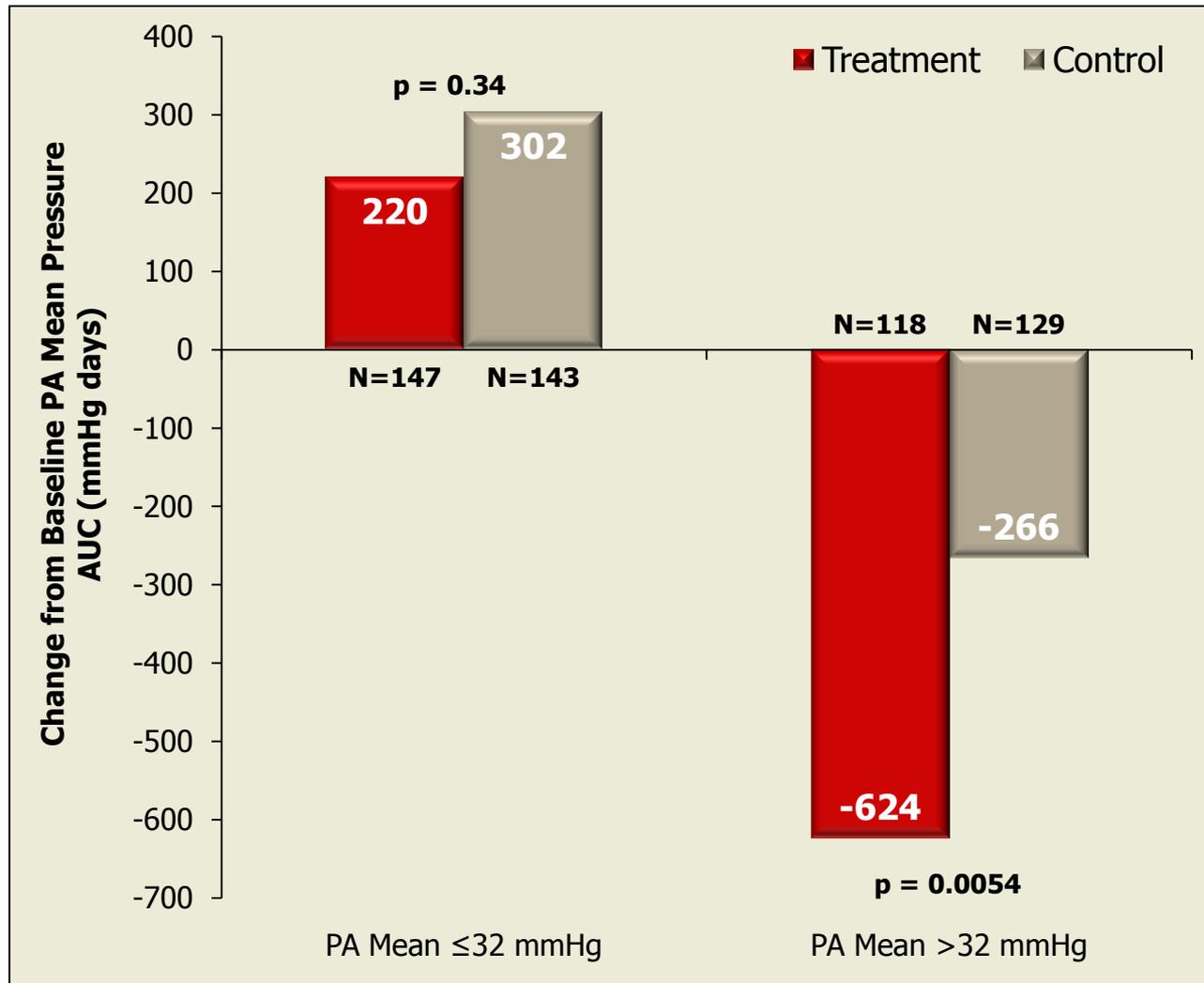
Sub-group Analysis of HF Hospitalizations Stratified by Gender

	Treatment			Control		
	Subjects	# Hosp.	Hosp. Rate (events/ patient-6 mo.)	Subjects	# Hosp.	Hosp. Rate (events/ patient-6 mo.)
Male	194	60	0.32	205	106	0.53
Female	76	24	0.32	75	14	0.19
Stratified Andersen-Gill, HR [95% CI] = 0.725 [0.549, 0.959], **p-value = 0.0240** [1]						
Interaction p-value = 0.001, Male p-value < 0.001, Female p-value = 0.008 [2]						
Female/Male Hosp. Rate ratio			1.00			0.36

[1] Results from Andersen-Gill Model, [2] Results from Negative Binomial Regression Model

- Significant effect of Treatment (p = 0.024) stratified by Gender
- Statistically significant interaction of gender and treatment
- Difference due to 3 patients and 10 hospitalizations (1 patient contributed 5)
- Hospitalization rate in women much lower than expected
- Low female control rate, literature suggests it should be similar to men
- More female deaths in control (7) vs treatment (3) complicate hospitalization rates

Kaplan-Meier Survival Analysis of Mortality for Female Patients
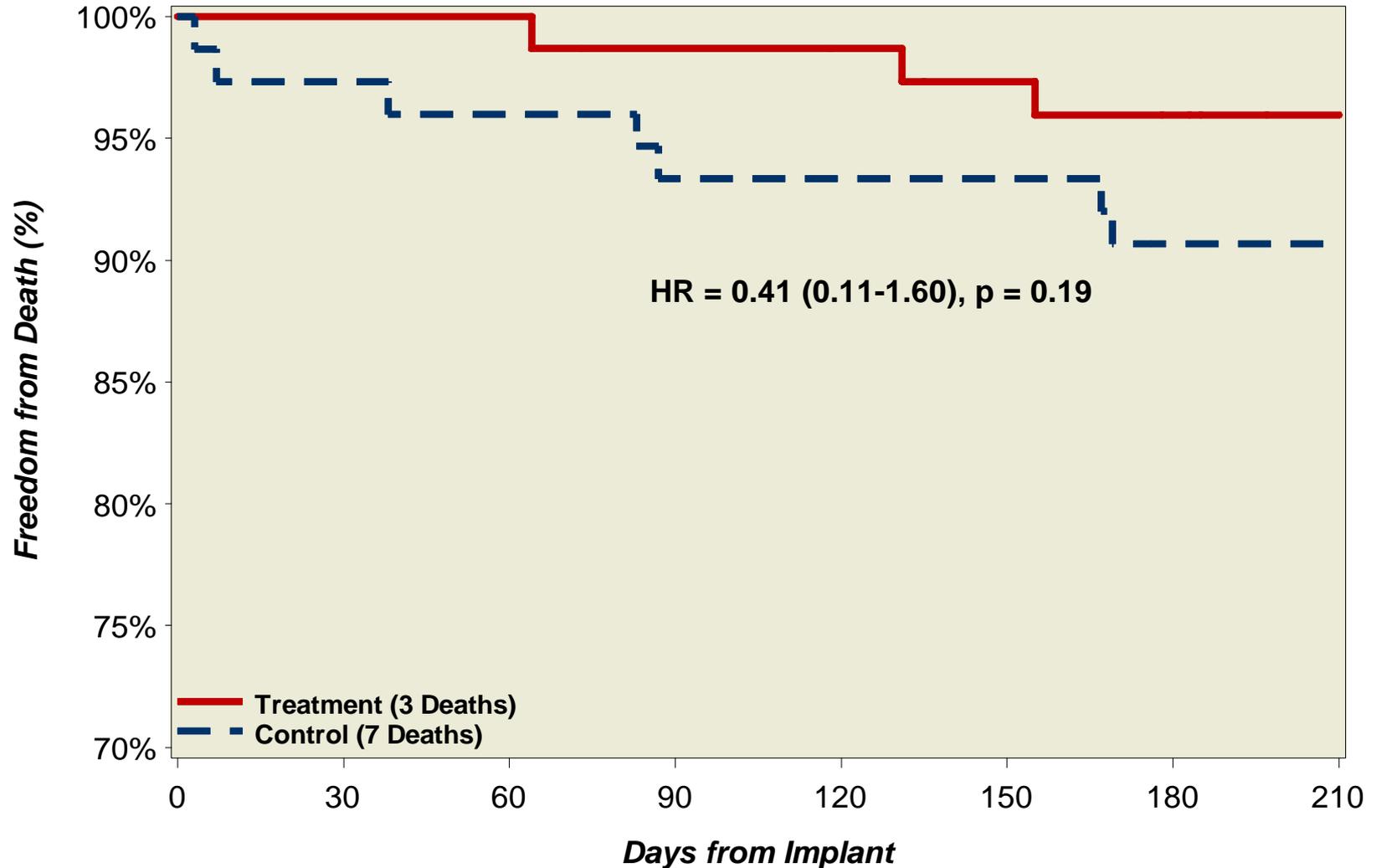
No. at Risk

Treatment	76	76	76	74	73	71	69	64
Control	75	73	72	70	70	70	66	64

Kaplan-Meier Analysis of 1st HF Hospitalization or Mortality for Female Patients

HR = 0.84 (0.42-1.68), p = 0.61

Treatment (15 Subjects with at least 1 HF Hospitalization or Death)
Control (17 Subjects with at least 1 HF Hospitalization or Death)

Days from Implant
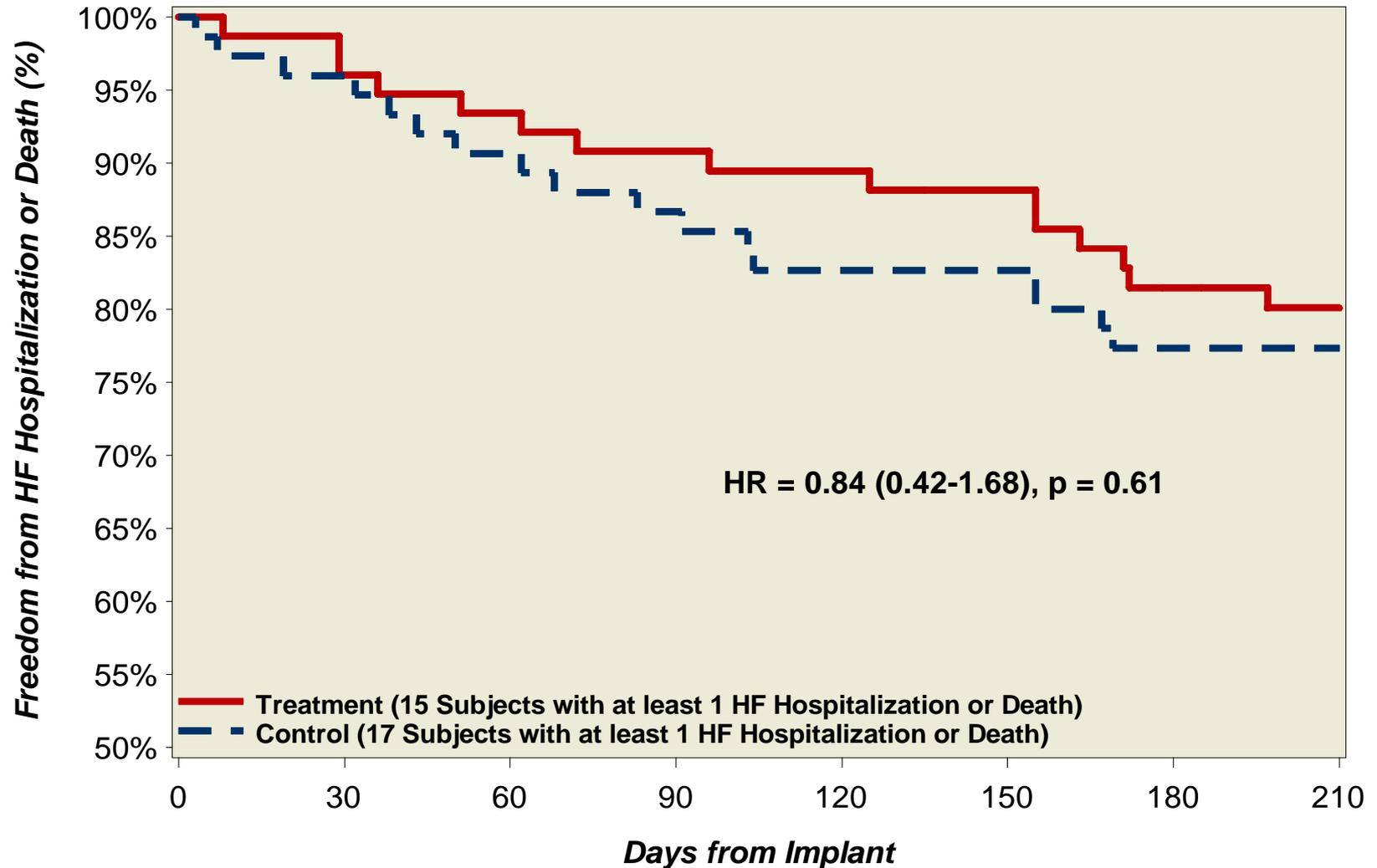
No. at Risk								
Treatment	76	73	71	69	68	66	59	54
Control	75	72	68	65	62	62	56	53

Composite Endpoint for <u>Males</u>
Freedom from at least 1 HF Hospitalization or Death

HR = 0.73 (0.55-0.97), p = 0.030

Treatment (84 Subjects with at least 1 HF Hospitalization or Death)
Control (107 Subjects with at least 1 HF Hospitalization or Death)
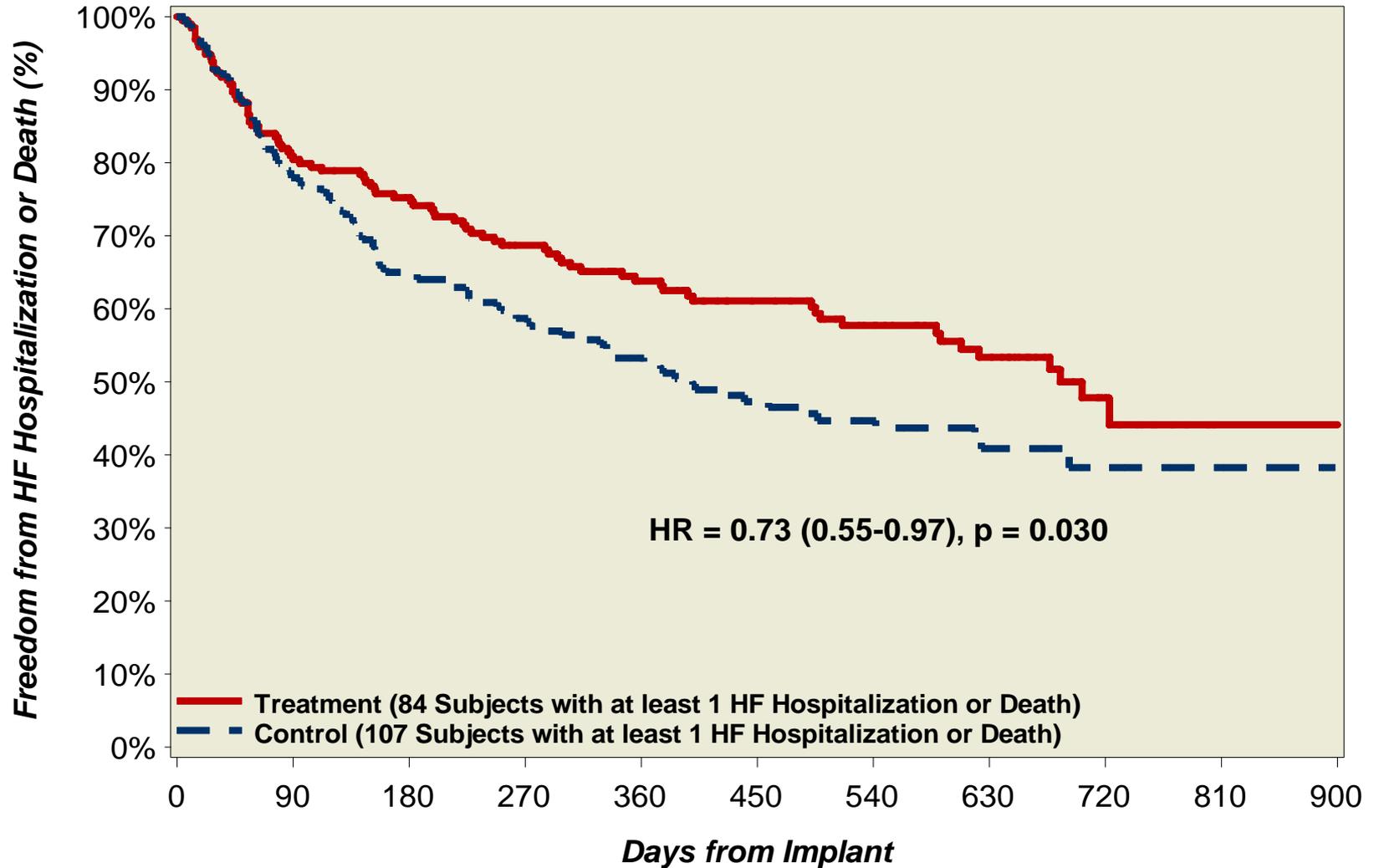
Days from Implant

No. at Risk											
Treatment	194	156	142	118	94	78	63	47	14	2	1
Control	205	158	130	106	81	57	42	28	11	4	0

P-values calculated using Log Rank Test

Multivariate Analysis of 6-Month HF Hospitalization or Mortality

| Baseline Predictors Remaining in the Model			Main Effects	
	Adjusted p-value	Hazard Ratio		Adjusted p-value
Age	**.011**	0.98	Gender	**.001**
Heart Rate	**.011**	1.02	Etiology	.333
Screening GFR	**.000**	0.98	Interactions	
Beta blocker dose	**.010**	0.99		Adjusted p-value
PVR	**.000**	1.13		
Gender	**.001**	0.48	Treatment x Gender	0.940
TREATMENT	**.013**	0.66	Treatment x Etiology	0.229

Results from Cox Regression.

- **19 Baseline Variables Considered in Model:**
  Age, gender, race, BMI, systolic BP, heart rate, creatinine, GFR, BUN, CRT/CRT-D, etiology of cardiomyopathy, cardiac output, ejection fraction, atrial fibrillation, diabetes, on ACE/ARB, beta blocker dose, cardiac index, PVR, and interactions: treatment x gender and treatment x etiology.

- **No Interaction with Gender or Etiology and TREATMENT Remains Significant**

HF Sensor Measurement Stability Over Time

Pressure Difference between the CardioMEMS Wireless HF Sensors and Reference Pressure Transducer over Simulated Time in the Cycle Test Fixture
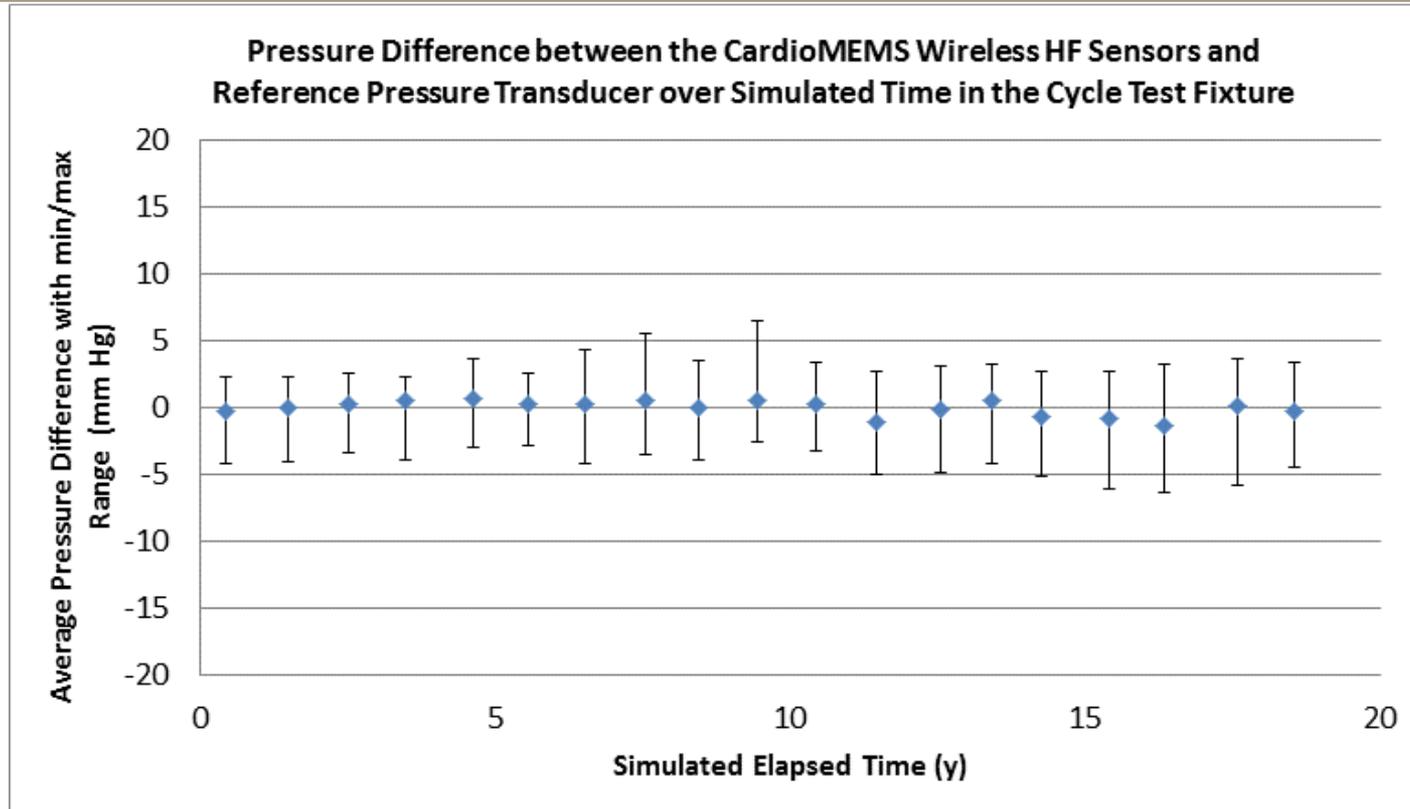
In laboratory testing, HF Sensors (n=7) were:
- Immersed in body temperature water (37 $^{\circ}$C)
- Exposed to >700 million representative cardiac pressure cycles, representing > 17 years of cardiac pressure cycles at 74bpm.
- Mean drift rate 0.027 ± 0.382 mm Hg / year

Sensor Performance in CHAMPION Clinical Study: Sources of Pressure Measurement Error in RHC

Sources of Swan-Ganz Mean Pressure Measurement Error:
- **Leveling:** Variation in transducer height
- **Transducer and Monitor:** Equipment accuracy
- **Digital Interpretation:** Variation in results of computer based waveform analysis
- **Waveform Artifact:** Variation in dynamic response of a fluid-filled system

1. A comparison of hydrostatic leveling methods in invasive pressure monitoring Rice, William; Fernandez, Edward; Jarog, Dena; Jensen, Alicia; *Critical Care Nurse;* Dec 2000
2. Phillips M8102A Technical Data Sheet
3. Comparison of pulmonary artery and central venous pressure waveform measurements via digital and graphic measurements methods. Ahrens, Thomas; Schallom, Lynn; *Heart & Lung;* Jan/Feb 2001
4. Accuracy and dynamic response of disposible pressure transducer-tubing systems. Hunziker, Peter; CAN J ANAESTH; 1987/34:4/pp409-14 [19% for systolic (6% for mean, CHAMPION PAM was 31mmHg)]
5. http://teacher.pas.rochester.edu/PHY_LABS/AppendixB/AppendixB.html [$\sqrt{(3^2 + 4^2 + 4^2 + 1^2)} = 6.5$]
6. See reference 5 [$\sqrt{(6.5^2 + 6.5^2)} = 9.2$]

Sensor Performance in U.S. Feasibility Study
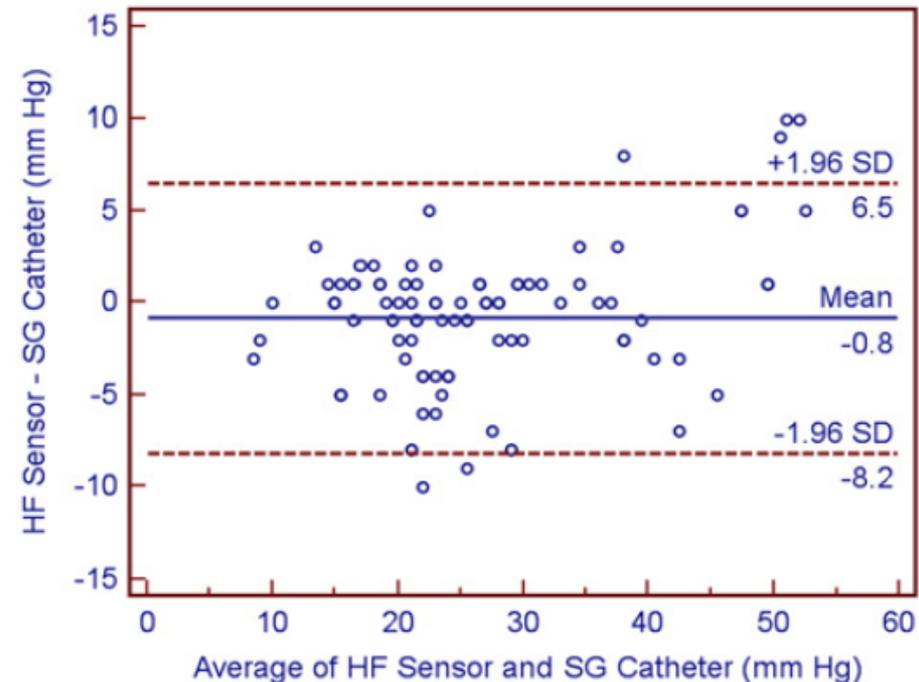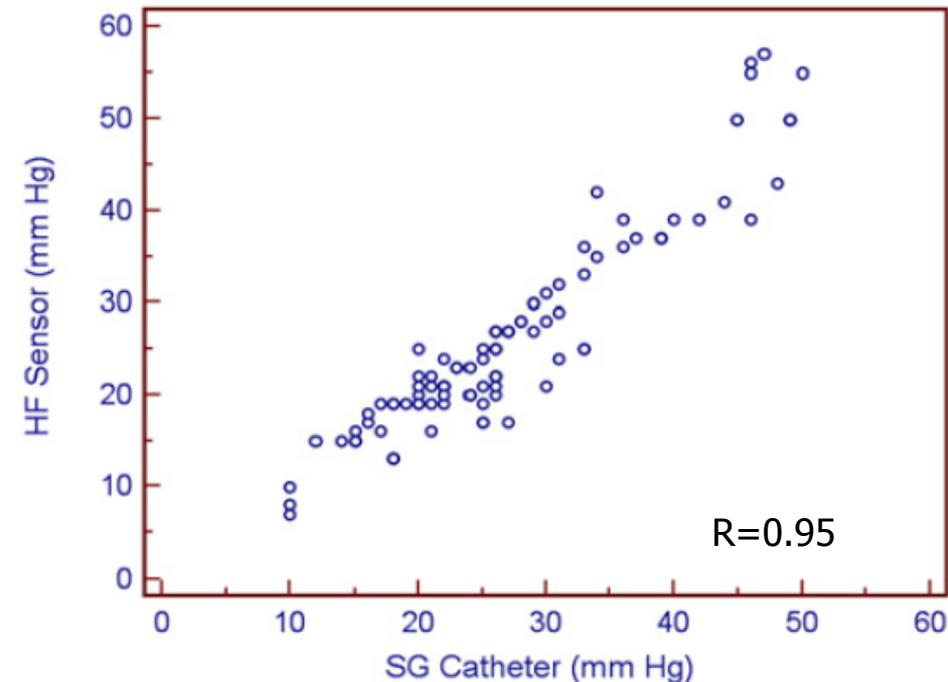
Safety and accuracy of a wireless pulmonary artery pressure monitoring system in patients with heart failure. Abraham WT, Adamson PB, Hasan A, Bourge RC, Pamboukian SV, Aaron MF, Raval NY. Am Heart J. 2011 Mar;161(3):558-66. Epub 2011 Jan 31.

Recalibration Summary

- During the study, there were 19 patients (11 Treatment, 8 Control) where sensor recalibrations were necessary

- 15 recalibrations were performed, 14 of which were identified prospectively

- Low rate of occurrence: 550 pts with >500,000 total patient days (1400 years)

- Root causes were determined and addressed as follows:

# Pts	Root Cause	Resolution	Effectiveness	
			# Implants Post Resolution	# Reoccurrences
9	Implant/RHC technique did not meet protocol specified requirements.	Implant/Catheter training reinforced. • Implant vessel size $\geq$7mm ID • No acutely angulated implant vessels (>30deg.) • No interference during follow up RHC.	178	0
8	Sensor testing and inspection criteria.	Refined testing and inspection criteria.	122	0
2	Incorrect sensor calibration at implant	Calibration training reinforced.	222	0

Sensor Performance in CHAMPION:
Correlation with RHC Over Time

- Follow-up data presented as measurement difference vs. time

- Follow-Up Duration: 265.0 $\pm$ 168.5 days (Mean $\pm$ SD)

- No observed deviation trend (drift) vs. time.