

Acorn CorCap™ Cardiac Support Device

FDA Review of P040049

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Mathematical Statistician, Division of Biostatistics

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Medical Director and Chief of Cardiothoracic Transplantation,
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Topics to be Presented

- Bram Zuckerman, M.D.
 - ◆ Intro to Device, Indications, File History
 - ◆ Intro to FDA Review of Acorn CorCap PMA
- William Maisel, M.D., M.P.H.
 - ◆ Summary of June 22, 2005 Advisory Panel Meeting
- Ileana Piña, M.D.
 - ◆ Clinical Review of Acorn CorCap PMA
- Laura Thompson, Ph.D.
 - ◆ Statistical Review of Acorn CorCap PMA
- Clyde Yancy, M.D.
 - ◆ Advisory Panel Member's Perspective
- Aron Yustein, M.D.
 - ◆ Conclusions and Recommendation

Introduction to FDA Review

Bram D. Zuckerman, M.D.

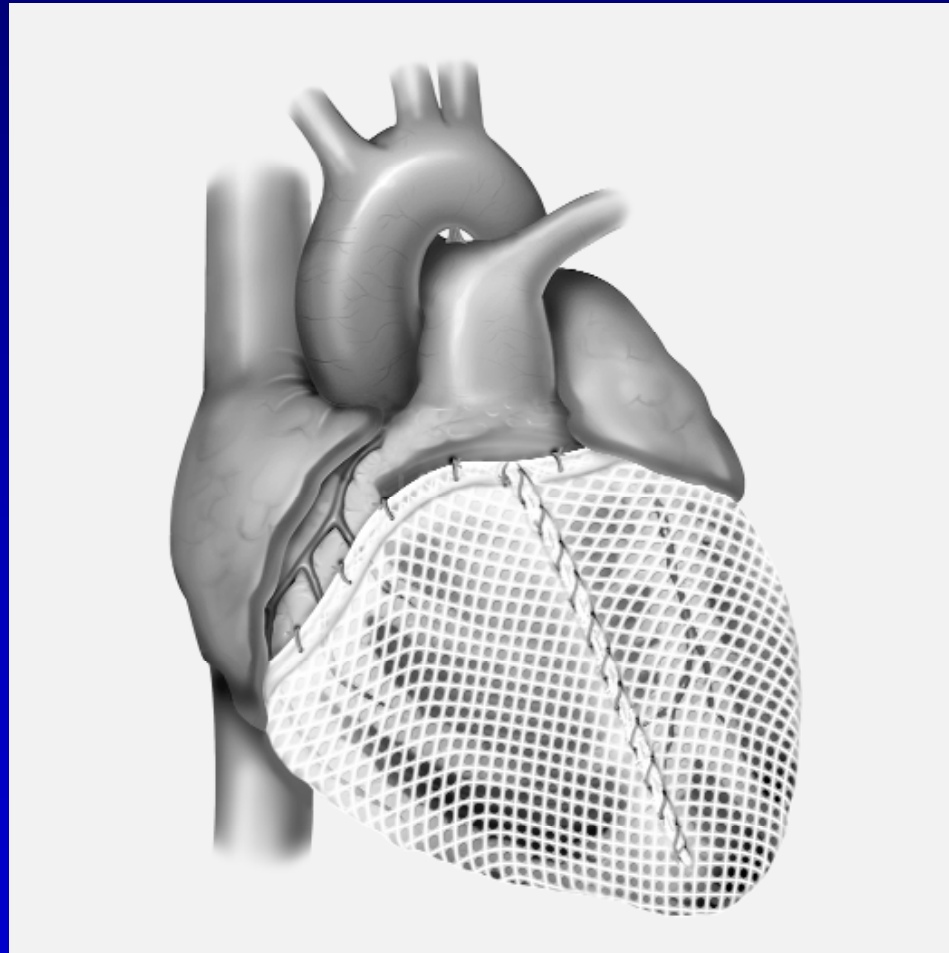
Director

Division of Cardiovascular Devices

Office of Device Evaluation

Center for Devices and Radiological
Health

CorCap Cardiac Support Device



Proposed Indications For Use

The CorCap CSD is indicated for use in adult patients:

- who have been diagnosed with dilated cardiomyopathy;
- are symptomatic despite treatment with optimal heart failure medical management;
- have a dilated heart (indexed left ventricular end-diastolic dimension (LVEDDi) ≥ 30 and ≤ 40 mm/m²); and
- have an LVEF $\leq 35\%$ (or LVEF $\leq 45\%$ if planned mitral valve repair or replacement).

History of Missing NYHA Data

- Acorn began enrolling patients at its own risk without agreement on primary endpoint
- Acorn changed assessment method for blinded NYHA during trial due to procedural/validity concerns
- FDA expresses concern regarding missing data in 41 patients already enrolled
- Acorn assures FDA this will not be a problem since baseline site assessments are done prior to randomization
- Due to sponsor's decision to continue enrolling patients throughout these discussions, 172 patients enrolled prior to implementation of the new blinded assessment of NYHA

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- 35% agreement between Site and Core Lab NYHA ($r = 0.16$)
- Acorn unsure what Core Lab NYHA is measuring, proposes to use Site NYHA at both time points
- FDA proposes imputation as a possible way to recover missing data
- Acorn rejects imputation, citing opinions of its advisors that imputing large amount of missing data not clinically valid
- FDA recommends that Acorn analyze NYHA component according to several methods and all analyses will be considered in review of PMA
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Outline of Post-Panel Interaction

- Advisory Panel voted 9-4 in favor of Not Approvable
- Acorn proposes to reanalyze data to address panel and FDA concerns
- FDA interested in identifying patient population where the risk-benefit profile is maximized
- FDA informed Acorn that we felt post hoc analysis would be hypothesis-generating for future study
- Not Approvable letter issued on August 12, 2005

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Focused Cohort Analysis

- *Post hoc* subgroup analysis
- A minimum of 152 combinations of baseline covariates and clinical outcomes were examined
- No new patient data provided since Advisory Panel
- Additional clinical data required to prospectively validate these findings
- Not Approvable letter issued on February 2, 2006

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2. Secondary endpoint results are problematic and not supportive of trial success
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Acorn CorCap™ Cardiac Support Device Summary of Panel Meeting June 22, 2005

William H. Maisel, MD, MPH
Chair, FDA Circulatory System Medical
Device Advisory Panel

Cardiovascular Division
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, MA

Circulatory System Device Panel

Acorn CorCap™ Cardiac Support Device

NOT APPROVABLE by **9 - 4** vote

- 15 participants – Diverse Expertise
 - Cardiac Surgeons
 - Interventional Cardiologists
 - Heart Failure Specialists
 - Statisticians
 - Consumer Representative
 - Industry Representative

Panel Concerns

- **Device Effectiveness**
 - Primary Endpoint
 - Secondary Endpoints
- **Safety**
- **Other Issues**
 - Missing Data
 - Subgroups

No ONE issue was the “Deal Breaker”
Absence of REASONABLE ASSURANCE
of Safety and Effectiveness

Primary Endpoint

NYHA Class/Major Cardiac Procedure/Death

Overview of Issues

NYHA: High rate of missing data, ? Clinical significance of core lab NYHA

Major Cardiac Procedures:

Driving force of Primary Endpoint Result

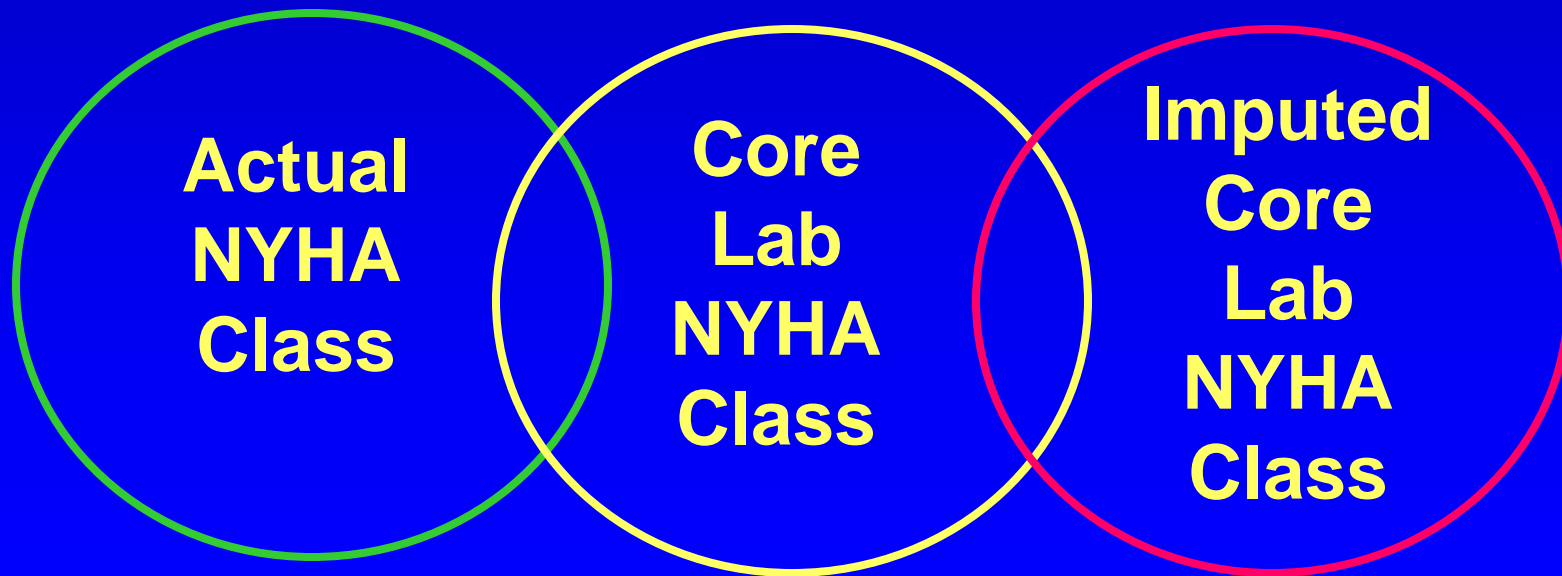
BUT BIASED

Death: No statistical difference in overall mortality but high early surgical mortality rate

Primary Endpoint

NYHA Class/Major Cardiac Procedure/Death

- Baseline data missing in 174/300
- Data imputed for 1^o endpoint in 104
- ? Clinical Relevance of “Core Lab” NYHA



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“...it is a lot of missing data...this is hard to assess”

- Dr. Brown, Sponsor Statistician

Primary Endpoint

NYHA Class/Major Cardiac Procedure/Death

- FDA vs. Sponsor Responsibility for Missing Data
 - Ultimately, sponsor's responsibility
 - Blame irrelevant – data must support SAFETY and EFFECTIVENESS

“...it is a lot of missing data...this is hard to assess”

- Dr. Brown, Sponsor Statistician

Primary Endpoint

NYHA Class/Major Cardiac Procedure/Death
(MVR/TVR/Bi V/LVAD/Transplant)

- Fewer in treatment c/w control
- Strong **BIAS** against intervening in CorCap group secondary to concerns about re-op, etc
 - Fewer transplant/VAD
 - Fewer repeat MV surgery
 - Fewer BiV
- BiV device included as major cardiac procedure
- Subjective decision making
- Adjudicated by blinded committee
BUT UNBLINDED DECISION MAKING

Primary Endpoint

NYHA Class/Major Cardiac Procedure/Death

- No Difference in Mortality
- Learning curve occurs over years
 - No MVR Stratum (Operative Mortality)
 - YEAR 1: 16.7% (2/12)
 - YEAR 2: 10% (2/20)
 - YEAR 3: 0% (0/19)
- Early Mortality Risk with CorCap

“I think we have a serious adverse event up front profile with this device”

- John Somberg, MD
Panel Member

Secondary Endpoints

Substantial Amounts of Missing Data

- **Objective measures of exercise**
 - Peak VO₂, 6 minute walk
 - Missing in sicker patients (NOT at random)
- **Measures of Ventricular Structure and Function**
- **BNP**
 - Higher in treatment than control
 - “sick” patients but 55% with BNP in normal range
- **QOL**
 - MLWHF, SF-36
- **All cause hospitalization**

Safety

- Early Mortality Risk
- Morbidity from Surgery
- Difficulty with Re-op

Safety

- Early Mortality Risk
- Morbidity from Surgery
- Difficulty with Re-op

Study patients are NOT “end-stage”

- 1/3 of Controls Got Better
- 55% BNP in Normal Range

Subgroups

- Ischemic vs. Non-Ischemic
 - Majority studied had non-ischemic CMP
 - Concern re: future revascularization in ischemics
- MVR vs. No MVR
 - “Clearly the operative mortality rate in the No MVR stratum was of concern”
 - Mariell Jessup
Co-PI, UPenn
Steering Committee ACORN CorCap
Clinical Trial

Subgroups

- Are Non-Ischemics Undergoing MVR a Viable Subgroup?
 - Effectiveness appears less in MVR vs. No MVR group
 - Study underpowered to detect important differences between groups
 - EF could be as high as 45% in MVR group c/w 30% in No MVR group

**NYHA
Missing
Data**

**? Clinical
Relevance
of Core
Lab NYHA**

**High
Early
Mortality**

**Primary
Endpoint
Issues**

**Poorly
Conducted
Study**

**?
Indicated
Population**

**Secondary
Endpoint
Missing
Data**

SAFETY and EFFECTIVENESS CONCERNS

**No
Mortality
Benefit**

**Constrictive
Physiology/
Pericarditis**

**Post Hoc
Data
Analysis**

**Biased
Unblinded
Procedural
Endpoint**

**Inconsistent
data re:
severity of HF**

Conclusions

NOT APPROVABLE by Panel Vote 9-4

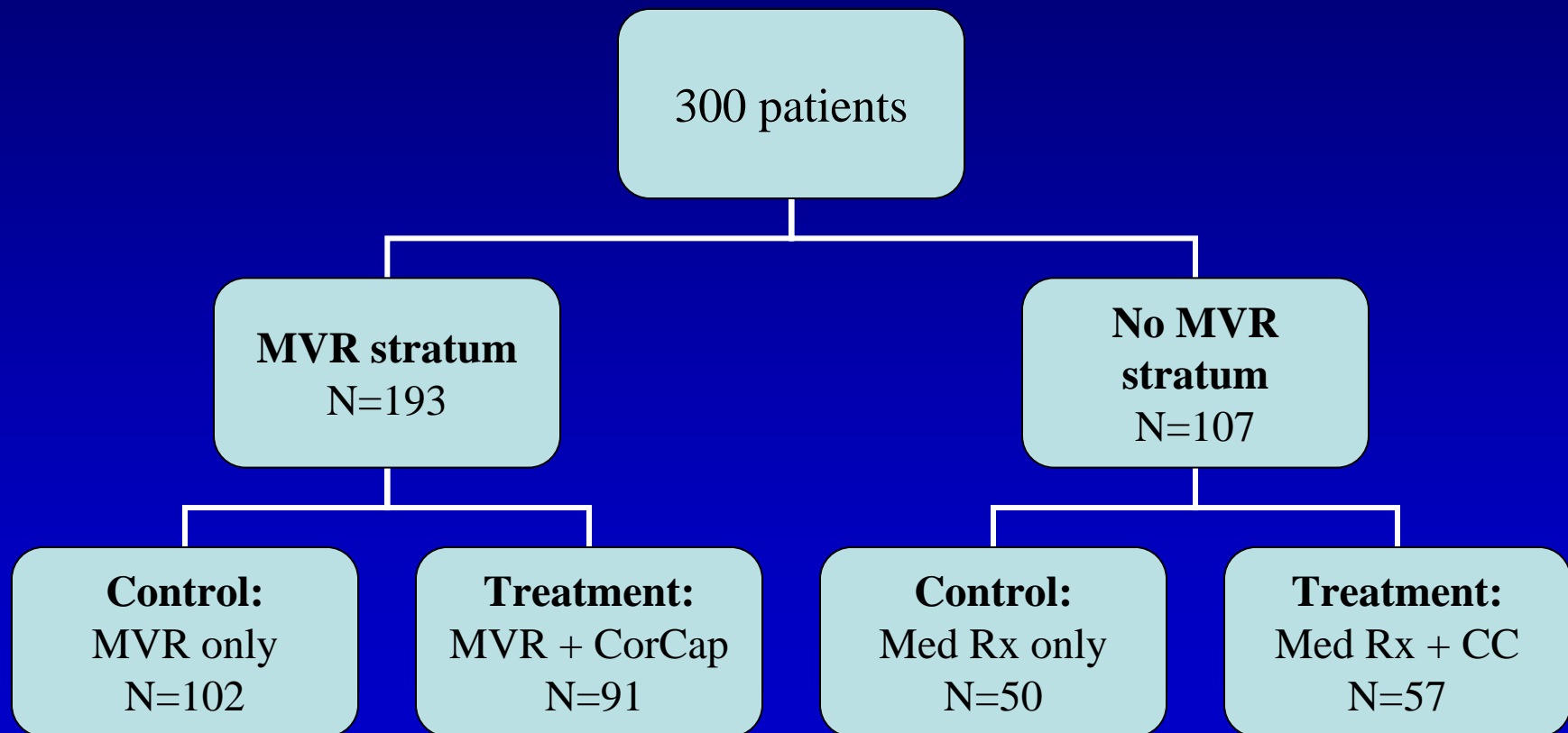
- Concerns about EFFECTIVENESS and SAFETY
- No One Issue was “Deal Breaker”
- Additional Data from Randomized Trial Needed to Support Approval

FDA Clinical Review of P040049

Ileana L. Piña, M.D., FACC, FAHA,
FACP

Professor of Medicine
Case Western Reserve University
Director, Heart Failure & Cardiac Transplant
VA Quality Scholar

Acorn CorCap Trial Design



CorCap Clinical Trial

- Hypothesis:

The CorCap would improve patient functional status as measured by a clinical composite consisting of

mortality

major cardiac procedure for worsening heart failure (MCP)

change in NYHA Class

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Baseline Comparison Between Site and Core Lab NYHA (N= 126)

	Core Class I	Core Class II	Core Class III	Core Class IV
Site Class I	0	0	0	0
Site Class II	1	2	15	8
Site Class III	0	5	40	51
Site Class IV	0	1	1	2

Pearson correlation coefficient 0.16

Different Methods For Analyzing Primary Composite Endpoint

Analysis Description	# Pts	Odds Ratio (95% CI)	p-value
Imputing the Missing Baseline Core Lab NYHA	293	1.73 (1.07, 2.79)	0.024
Patients with an Outcome for Primary Endpoint	191	1.57 (0.89, 2.79)	0.12
Compare Site-Assessed NYHA at Baseline and Follow-Up	290	1.51 (0.96, 2.37)	0.07
Compare Site-Assessed NYHA at Baseline with Core Lab NYHA at Follow-Up*	293	1.45 (0.91, 2.30)	0.12

* Final Protocol-Approved Primary Endpoint Analysis Plan
Table 1 from Executive Summary

Different Methods for Analyzing NYHA Component (average change over time)

Analysis Method	# Pts	Average Treatment Difference (T-C)	p-value
Imputing the Missing Baseline Core Lab NYHA	293	-0.07 class	0.38
Patients with Core Lab NYHA at Baseline and Follow-Up	126	-0.08 class	0.49
Compare Site-Assessed NYHA at Baseline and Follow-Up	293	-0.04 class	0.60
Compare Site-Assessed NYHA at Baseline with Core Lab NYHA at Follow-Up	293	-0.02 class	0.80

Modified Table 2 from Executive Summary

Cumulative Mortality (as of Dec 30, 2005)

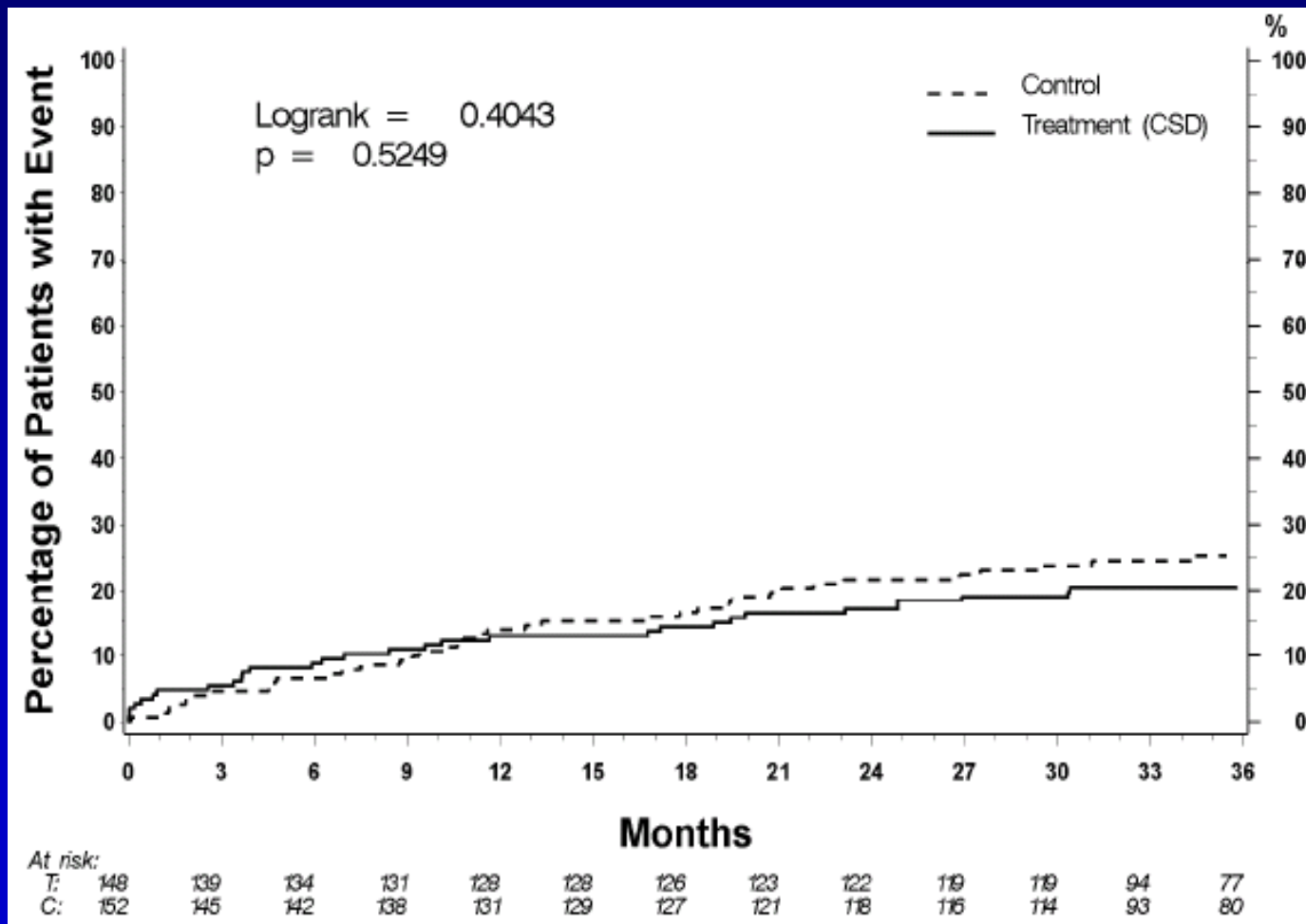


Figure 1 from Executive Summary

Major Cardiac Procedures

- Major Cardiac Procedures (MCP) were defined as surgical interventions for worsening heart failure including CABG, MVR, TVR and BiV pacing.
- Progression of heart failure
 - ◆ Hx and P.E.
 - ◆ Decreased exercise tolerance, JVD, rales
 - ◆ CXR
 - ◆ Laboratory Studies
 - ◆ Right Heart Catheter
 - ◆ Lack of Clinical Response to Conservative Rx

Major Cardiac Procedures by Subgroup: CRT (BiV Pacing) vs. Open Procedures

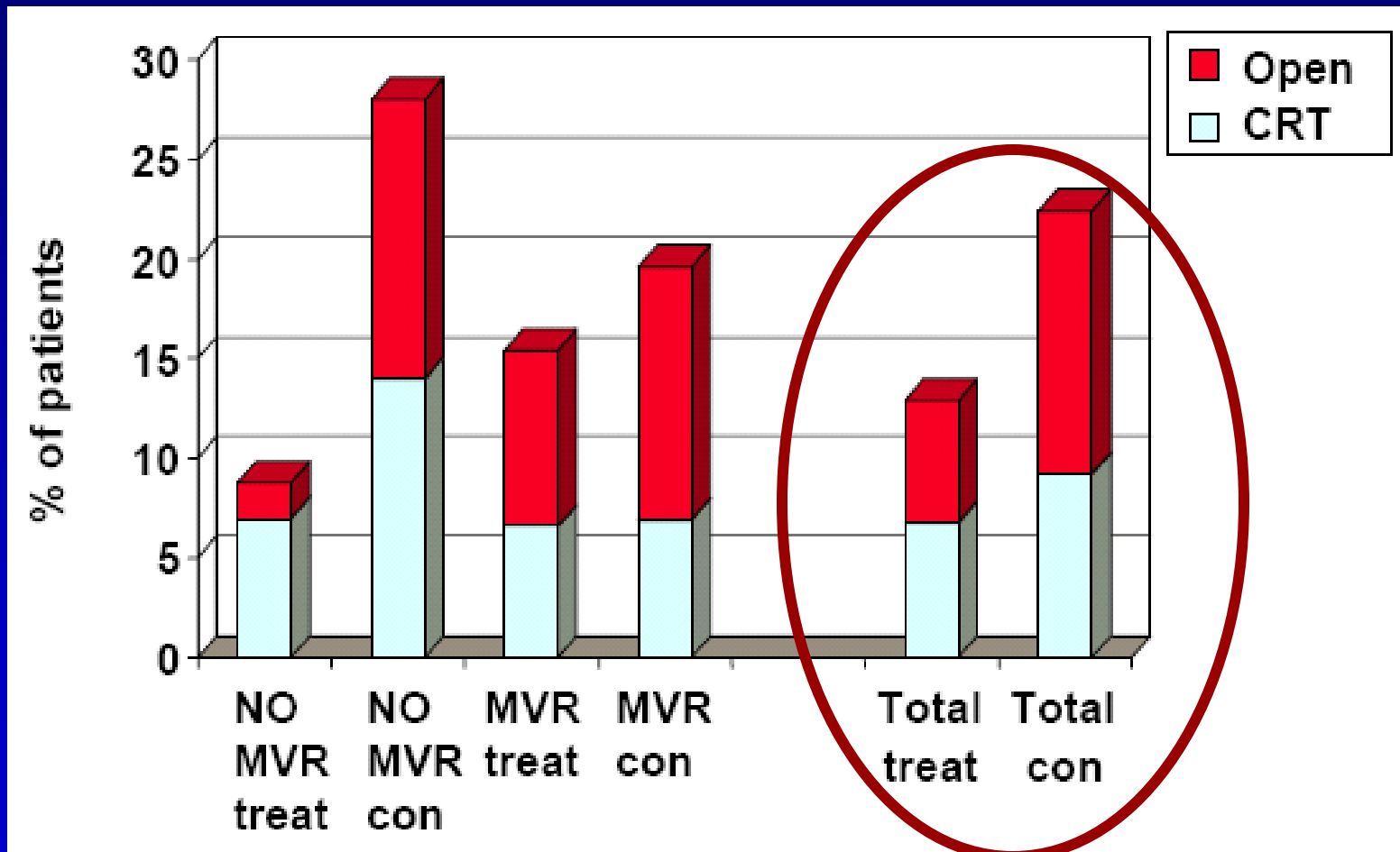


Figure 3 from Clinical Summary

Major Cardiac Procedures by Subgroup: CRT (BiV Pacing) vs. Open Procedures

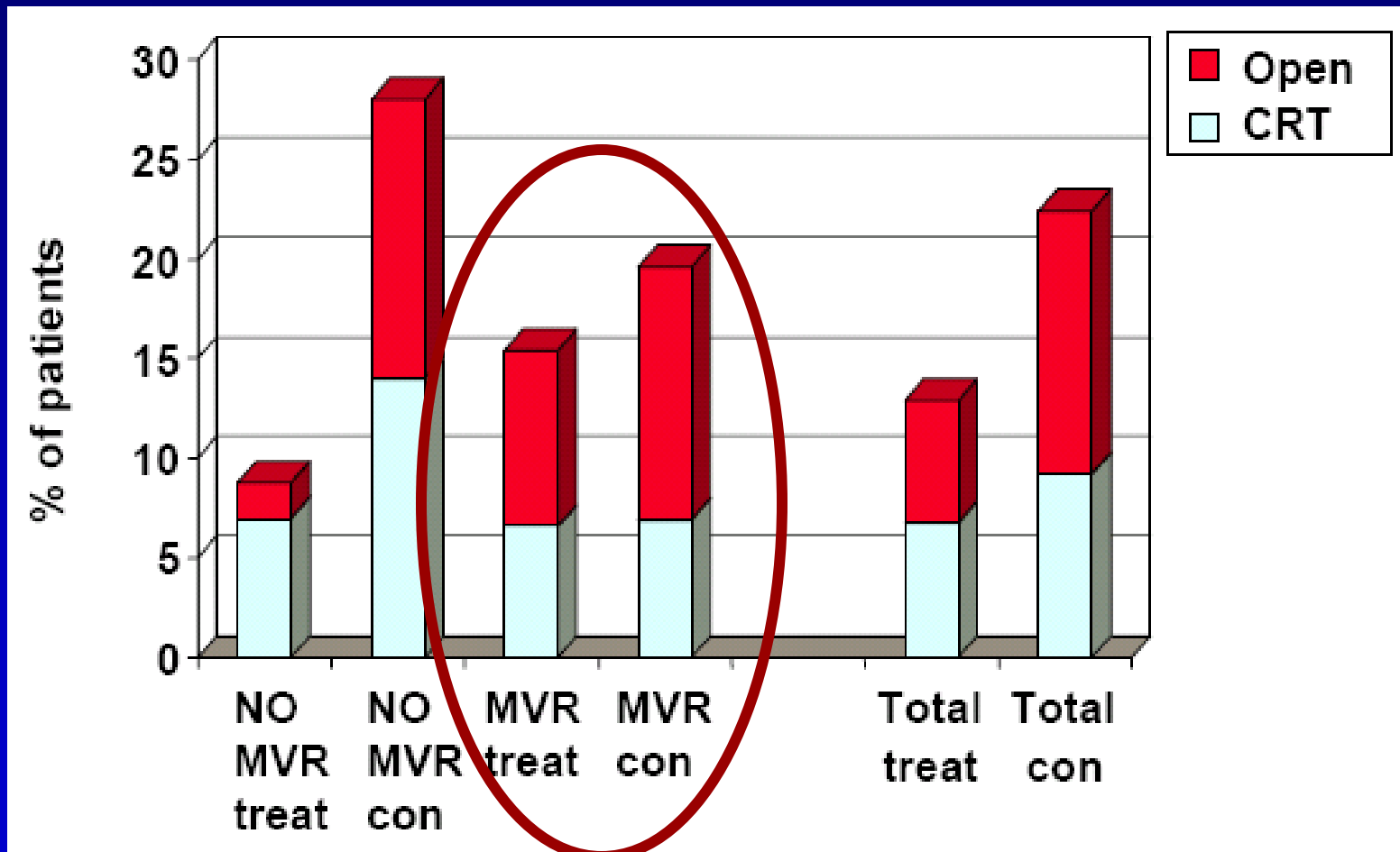


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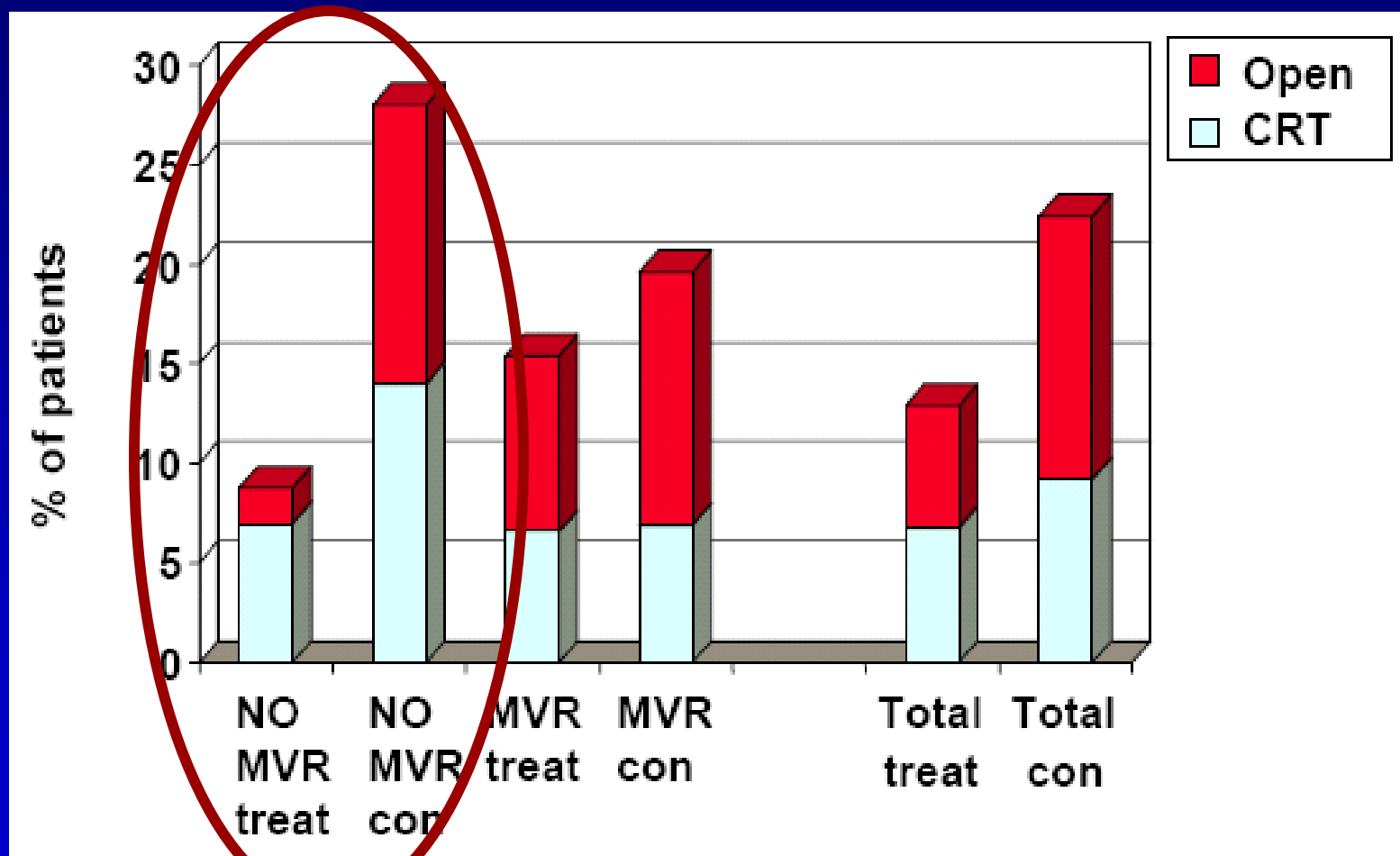


Figure 3 from Clinical Summary

Primary endpoint result is not interpretable

- 35% of patients missing an outcome for the primary endpoint
- Core Lab NYHA questionnaire lacks validity
- Substituting Site NYHA yields an insignificant result
- No observed benefit in mortality or NYHA
- MCP component in the No MVR group is only sign of potential clinical benefit and may be subject to treatment bias and placebo effect

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Major Secondary Endpoints

Endpoint	Observed Treatment Difference (T-C)	Adjusted Hochberg p-value
LVEDV	-17.9 ml	0.032
LVEF	0.83%	0.60
MLHF	-4.47 points	0.146
NYHA (Site Assessed)	-0.04 class	0.60

Modified Table 3 from Executive Summary

Clinically Meaningful vs. Observed Treatment Differences in Secondary Endpoints

Endpoint	Sponsor's Proposed Clinically Meaningful Treatment Difference (T-C)	Actual Observed Treatment Difference (T-C)
LVEDD	-4 mm	-1.8 mm
LVESD	-4 mm	-1.2 mm
NYHA (Core Lab)	-0.5 class	-0.07 class
MLHF	-11 points	-4.47 points
6-Minute Walk	40 meters	-21.8 meters†

† Favors Control

Table 4 from Executive Summary

6 Minute Walk – Average Change over Time (Using Available Data)

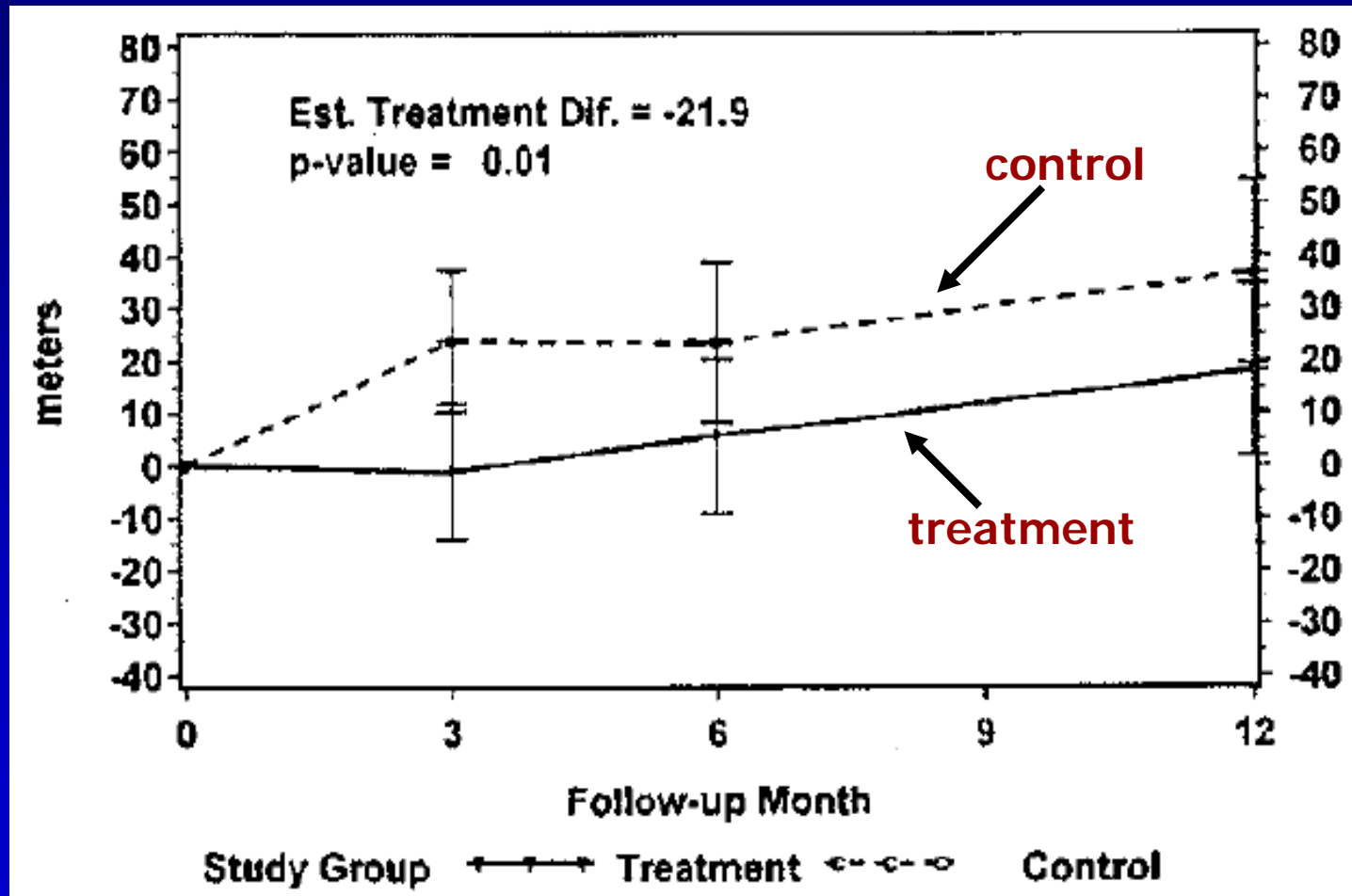


Figure 4 from Clinical Summary

Peak VO₂ – Average Change over Time (Using Available Data)

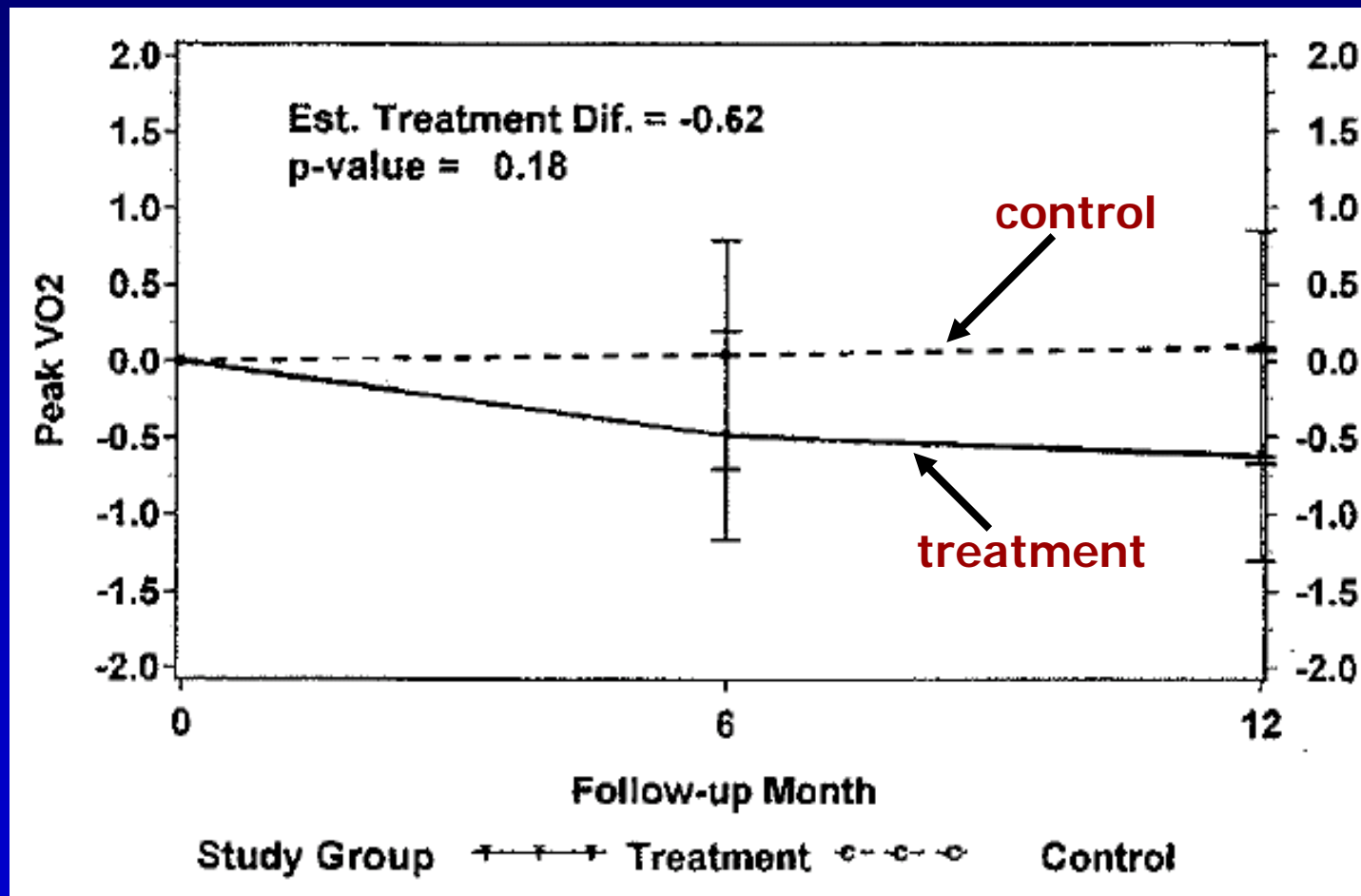


Figure 5 from Clinical Summary

Structural Endpoints – Average Change Over Time (Using Available Data)

Structural Endpoints	Treatment Difference (T-C)	Unadjusted p-value
LVEDV	-17.9 ml	0.008
LVESV	-15.2 ml	0.02
LVEF	0.83%	0.49
Sphericity Index	0.042	0.031
Mass Index	-5.9 g/m ²	0.15
LVEDD	-1.8 mm	0.02
LVESD	-1.2 mm	0.21

Table 6 from Executive Summary

Missing Data in Secondary Endpoints at 12 Months

Secondary Endpoint	Treatment	Control
LVEDV, LVESV, LVEF	16%	24%
Cardiac Sphericity	15%	22%
LV Mass	38%	39%
LVEDD, LVESD	7%	11%
6 Minute Walk	18%	34%
Peak VO ₂	35%	49%

Combined Tables 5 and 7 from Executive Summary

Correlation b/w changes in structure (LVEDV) and function (6MW, Peak VO₂, NYHA)

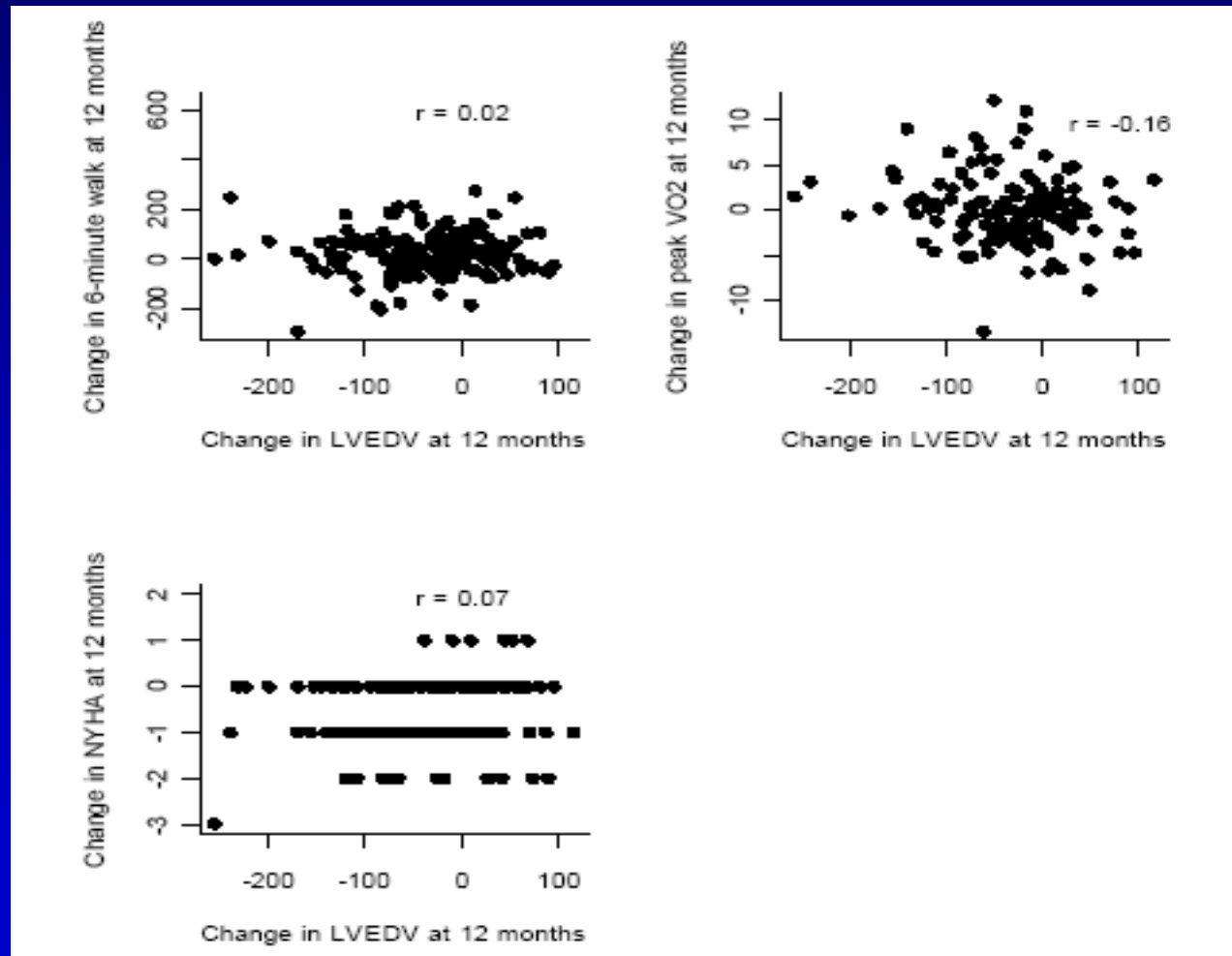


Figure 2 from Executive Summary

Secondary endpoint results are problematic and not supportive of trial success

- Lack of clinical or statistical significance in a majority of key structural and functional measures
- Large amount of missing data for several secondary endpoints
- Available data favor the Control group for objective functional endpoints
- Low correlation between changes in structure and function

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Safety Concerns

- High perioperative mortality 4/51 (7.8%) in CorCap (0/50 control) in the No MVR group
 - ◆ 95% CI for "Treatment – Control" was 0.2% to 19% in the No MVR group
- Re-operation in CorCap patients
 - ◆ Vivid descriptions of dense adhesions and procedural difficulty in 7/8 operative reports for patients with CorCap
 - ◆ 12/22 operative reports for MVR Control patients also included reference to adhesions, but not in such great detail
- CorCap patients ineligible for future CABG
- Pericardial constriction

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Components of Primary Endpoint Analyzed by Strata

Component	Odds/Hazard Ratio (T/C)	p-value
No MVR Stratum		
Mortality	Not Provided	0.71
Major Cardiac Procedures	0.28	0.02
Core Lab NYHA [*]	2.37	0.16
MVR Stratum		
Mortality	Not Provided	1.0
Major Cardiac Procedures	0.57	0.11
Core Lab NYHA [*]	1.45	0.35
All Patients		
Mortality	Not Provided	0.83
Major Cardiac Procedures	0.46	0.009
Core Lab NYHA [*]	1.64	0.12

Table 9 from Executive Summary

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FDA Statistical Review of P040049

Laura Thompson, Ph.D.

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FDA Concerns with Acorn PMA

1. **Primary endpoint result not interpretable**
2. **Secondary endpoint results are problematic and not supportive of trial success**
3. Safety concerns raised by FDA and Advisory Panel are not adequately addressed
4. Risk-benefit profile not acceptable in either the MVR or No MVR strata
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Primary Endpoint

- **Composite Endpoint** (evaluated > 12 months)
 - ◆ all-cause mortality
 - ◆ change in core lab NYHA class assessment from baseline
 - ◆ major cardiac procedures indicative of worsening HF
- **Ordinal Scoring** (1=Improved, 2=Same, 3=Worsened)
 - ◆ *Improved* = Improved NYHA class and did not die and did not receive MCP
 - ◆ *Same* = no change in NYHA from baseline, did not die and did not receive MCP
 - ◆ *Worse* =
 - ◆ Died, or
 - ◆ Received MCP for worsening HF, or
 - ◆ Worsened on NYHA class

Missing Data in Primary Endpoint: Statistical History

- Trial enrollment had begun prior to agreement on the primary endpoint.
- 58% of patients did not have a baseline core lab NYHA assessment.
- Possible replacement using Site-assessed NYHA, assessed prior to randomization.

Analysis of Primary Endpoint

Analysis Description	# Pts (CorCap; Control)	Odds Ratio (95% CI)	p-value
Imputing the Missing Baseline Core Lab NYHA	293 (147; 146)	1.73 (1.07, 2.79)	0.024
Patients with Baseline Core Lab NYHA	121 (61; 60)	1.75 (0.86, 3.56)	0.12
Compare Site-Assessed NYHA at Baseline and Follow-Up	290 (145; 145)	1.51 (0.96, 2.37)	0.07
Compare Site-Assessed NYHA at Baseline with Core Lab NYHA at Follow-Up	293 (147; 146)	1.45 (0.91, 2.30)	0.12

Missing Data in Primary Endpoint: Statistical History

- Agreement between Site-assessed NYHA and Core Lab NYHA is low.
- Replace Core Lab NYHA with (unblinded) Site-assessed NYHA at both baseline and follow-up?

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Missing Data in Primary Endpoint: Statistical History

- FDA proposed multiple imputation as a way to handle the missing data.
- Data appeared to be missing at random, due to a design feature (unavailable baseline NYHA instrument), and not apparently due to outcome.
- FDA also requested to see the primary endpoint analysis, using complete data.

Missing Data in Primary Endpoint: Statistical History

- Sponsor rejected the recommendation to use imputation.
- Two months after data were unblinded, Sponsor agreed to use imputation.
- FDA feels that it is important to decide on the primary analyses for a clinical trial prior to data unblinding.

Imputation Models

- **Imputation Models:** Regression of baseline blinded core lab NYHA on observed variables
- Multiple imputation techniques
- Missingness assumed at random (MAR)
- 36% (54/148) of CorCap and 32% (48/152) of Control primary endpoint values were based on imputation.

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Separate Analyses of Components of Primary Endpoint

Which components contribute relatively more to the overall composite?

Mortality Component

- Log-rank test of difference in KM survival curves $p = 0.85$

Cumulative Number of Deaths by Time

Follow-up	CorCap N=148	Control N=152	95% CI on Trt-Control Difference
30 Days	7 (4.7%)	1 (0.7%)	(0.3%, 9.0%)
12 months	19 (12.8%)	21 (13.8%)	(-9.0%, 7.0%)
24 months	22 (14.9%)	24 (15.8%)	(-9.0%, 8.0%)
Up to CCD	25 (16.9%)	25 (16.4%)	(-8.0%, 9.0%)

MCP Component

CorCap	Control	CMH Odds Ratio (95% CI)
19/148 = 12.8%	33/152 = 22%	2.22 (1.16, 4.20) p = 0.014

Includes patients who ultimately died
(CorCap: 3; Control: 5)

NYHA Component

Analysis Method	# Pts	Average Treatment Difference (T-C)	p-value
Imputing the Missing Baseline Core Lab NYHA	293	-0.07 class	0.38
Patients with Core Lab NYHA at Baseline and Follow-Up	126	-0.08 class	0.49

Modified Table 2 from Executive Summary

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Four Pre-specified “Major” Secondary Endpoints

- LVEDV, LVEF, MLHF, site-assessed NYHA
 - ◆ Hochberg procedure was prospectively proposed for these endpoints to control familywise type I error rate at 5%
 - ◆ Hochberg procedure is used to adjust the *individual* p-values for multiplicity.

Multiple Secondary Endpoints: A Reminder

- If and only if the primary endpoint is met, pre-specified multiple secondary endpoints are tested as a family at an additional overall significance level.
- Each endpoint in the family can use the 0.05 criterion for declaring significance, after its p-value is adjusted for multiplicity.

Multiple Secondary Endpoints: A Reminder

- For any additional secondary endpoints (for which multiple testing issues were not considered a priori), statistical significance cannot be interpreted for regulatory considerations.
- After performing the Hochberg procedure on 4 pre-specified major secondary endpoints, with significance level of 0.05, the sponsor has exhausted their type I error rate allotment for secondary endpoints.
- No additional secondary endpoints can be declared significant.

Major Secondary Endpoints

Major Secondary Endpoint	Difference in mean change from baseline over time (CorCap – Control)	Adjusted p-values
Site NYHA	-0.04	0.60
LVEF	0.83%	0.60
MLHF	-4.47	0.146
LVEDV	-17.9	0.032

Only the p-value for LVEDV, a structural endpoint, can be considered statistically significant, according to the Hochberg Procedure.

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Focused Cohort Analysis

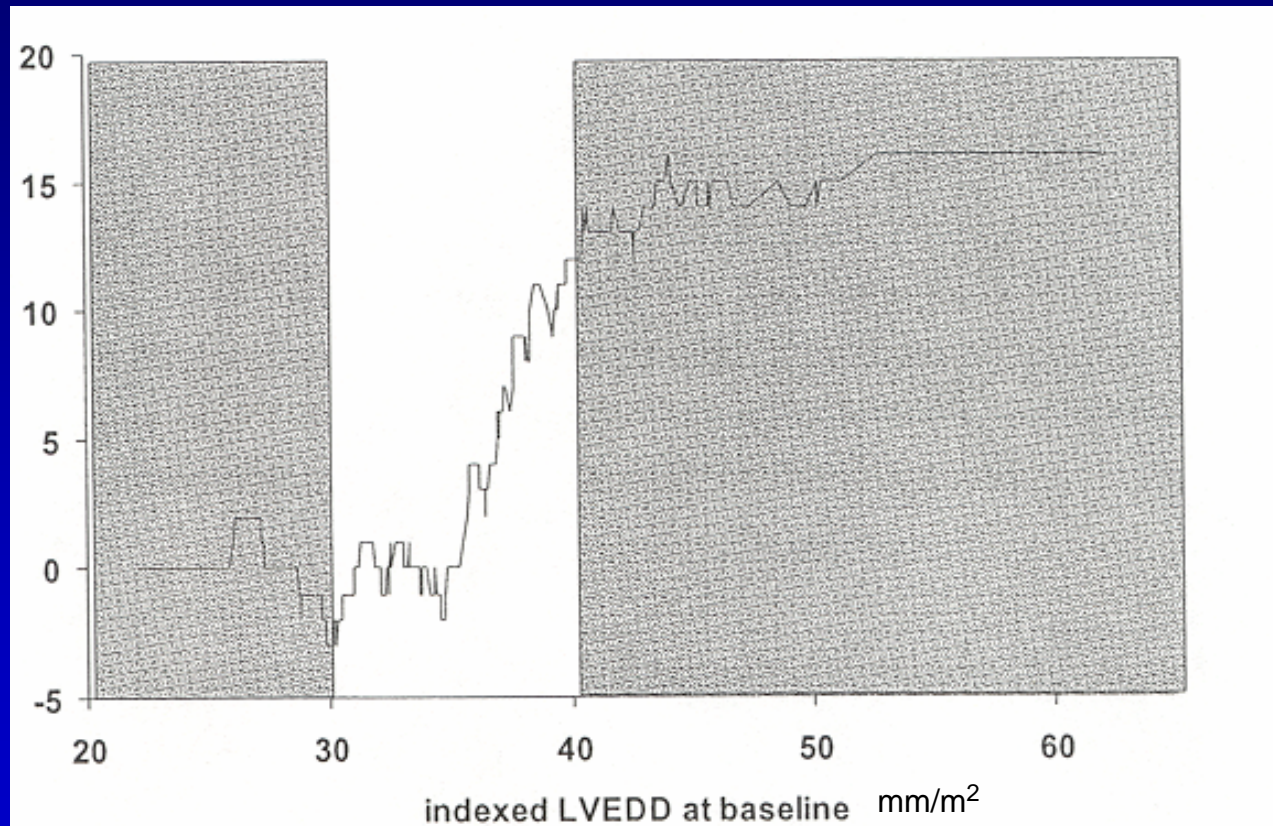
- The sponsor has identified a subgroup that they claim benefits most from the CorCap, and excludes high-risk patients.
- However, the sponsor has used the same data to choose the cohort, as well as to do statistical testing on the cohort.
- This increases the risk of a finding that occurs purely by chance (false positive).
- This analysis cannot be used reliably as a basis for approval.

Identifying the Focused Cohort: An Overview

- After examining a minimum of 19 covariates, and their relationship with 8 clinical outcomes, the sponsor selected the subgroup that achieved the highest “Treatment – Control” difference on the primary endpoint.
- This subgroup is the “focused cohort.”

Identifying the Focused Cohort

Cumulative
Treatment-
Control
Difference
in mortality



LVEDDi between 30 and 40 was chosen as the "focused cohort."

Primary endpoint analysis using chosen subgroup => $p = 0.01$ 103

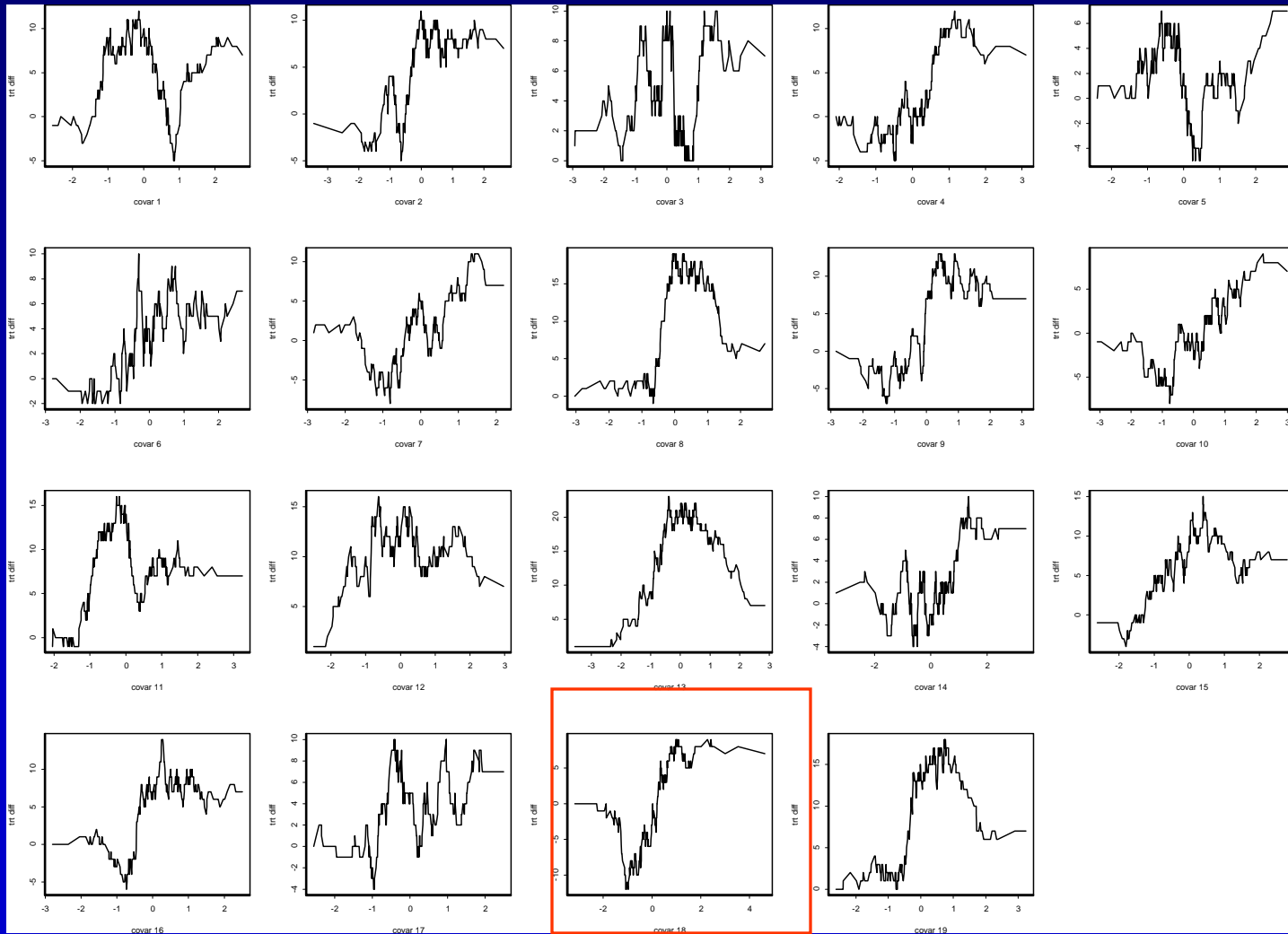
FDA Concerns with Analysis of the Focused Cohort

- Choosing a Focused Cohort based on cumulative trends analysis is equivalent to choosing a “best” subgroup based on p-values from primary analysis.
- Essentially, a hypothesis was chosen using data that was later used to test the hypothesis.
- For the sponsor’s analysis, many subgroups were examined prior to choosing the best.
- Increased risk of type I error rate.

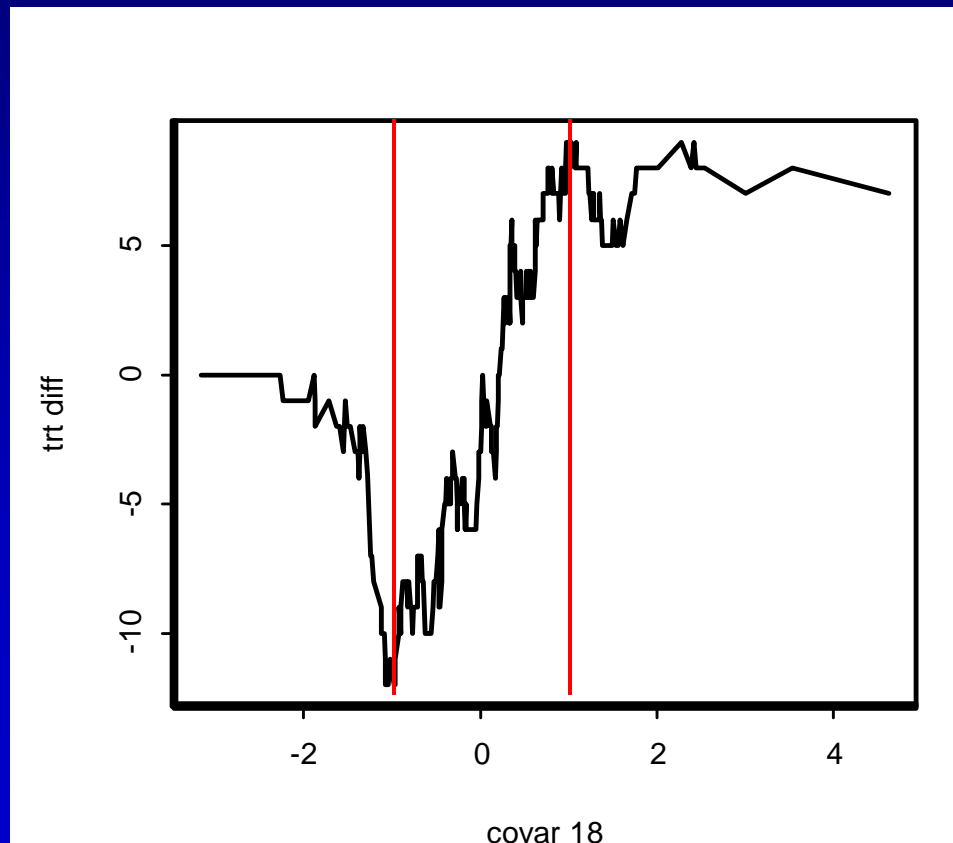
Simulation of Sponsor's Analysis Under No Treatment Difference

- Simulated 300 binary outcomes, with failure rate = 0.40
- Randomly assigned 1:1 to two treatment groups
- Null hypothesis of no treatment difference is true.
- 19 independent covariates simulated from a standard Normal distribution, for each "patient".

"Significant Result" Can be Easily Found When There is No Treatment Difference



“Significant Result” Can be Easily Found When There is No Treatment Difference



2-sample test
for equality of
proportions:
 $p = 0.028$

Summary of Statistical Concerns

- Large amount of missing data in primary endpoint, due to sponsor's decision to enroll patients prior to agreement on primary endpoint.
- Examination of separate components of composite shows strong influence of reduction in MCPs for the CorCap group.
- There was no difference in mortality trends across CorCap and Control.

Summary of Statistical Concerns (continued)

- There was no significant difference in change-in-NYHA.
- Results from major secondary analyses found statistically significant CorCap benefit for structural, but not functional endpoints.
- Results from post-hoc analysis of Focused Cohort are good for offering some insights into *future studies*, but not sufficient to provide valid scientific evidence to support device approval.

Advisory Panel Member Perspective

Clyde W. Yancy, M.D., FACC, FAHA,
FACP

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Baylor University Medical Center
Heart and Vascular Institute
Dallas, TX

Disclosure Information

- My employer is:
 - ◆ Baylor University Medical Center, Heart and Vascular Institute, Dallas, TX
- I am a consultant for:
 - ◆ Astra-Zeneca, CHF Solutions, GlaxoSmithKline, Medtronic, Nitromed, Novartis and Scios, Inc.
- I hold no single company pharmaceutical or device company stocks
- I have received research support from:
 - ◆ GlaxoSmithKline, Medtronic, Nitromed, Scios, Inc.
- I have accepted honoraria from:
 - ◆ GlaxoSmithKline, Medtronic, Novartis, Scios

Slide 111

S4

Dr Yancy, please complete this slide as per HFSA guidelines. Thank you!
S&H, 8/8/2006

Introduction

- The burden of heart failure
- Effectiveness of current medical/device therapy
- Establishing the need for new therapies; targeting reverse remodeling
- Demonstrating safety and effectiveness of new treatments

Acorn CorCap[®] CSD

- What was the rationale?
- What is the premise?
- Was a mechanism of action demonstrated?
- What were the issues regarding data interpretation that impacted the original panel? Have those questions been resolved?
- If approved, how do we write a label indication?

The Rationale?

- NYHA Class III/IV has limited treatment options:
- *However:*
 - ◆ ACE-inhibitors; reduce mortality in class IV heart failure; CONSENSUS
 - ◆ BETA-blockers; reduce mortality in class III HF and in patients with an LVEF as low as 0.15; COPERNICUS
 - ◆ Aldosterone antagonists; reduce mortality and sudden death in class III/IV HF; RALES
 - ◆ ISDN/HYD; reduces mortality by 43% in class III HF; A-HeFT
 - ◆ CRT; reduces mortality by 30% in class III HF; CARE-HF
 - ◆ ICD; reduces mortality by 23% [over 5 years]; SCD-HeFT
 - ◆ Beta-2 agonists; may recover ventricular function with LVAD support in inotrope dependent class IV HF; Yacub et al

The Premise?

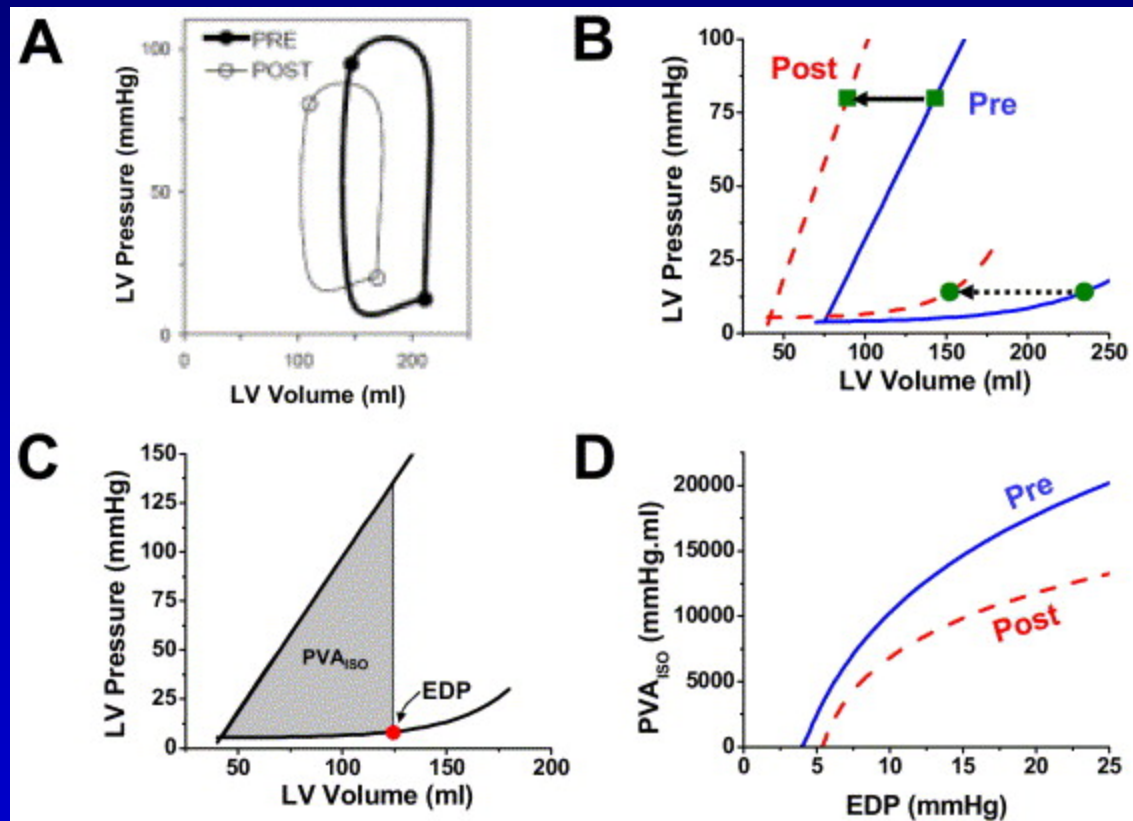
- Surgical constraint of the left ventricle results in a decrement in LV size, reduces neurohormonal activation, reverses an abnormal growth stimulus and induces reverse remodeling
- *Is this a good thing??*

Lessons learned from SVR operations

- Resection of a portion of the left ventricle can detrimentally affect diastolic chamber properties
- The effect of such a procedure on overall pump function reflects the balance of its effects on systolic and diastolic properties
- Mechanism: the shift in end-systolic pressure volume relationships is greater for diastole than systole, yielding an *increase in chamber stiffness*; EF increases because of a change in EDV [i.e., $SV/EDV=EF$] but SV does not increase
- Message; surgical reverse remodeling may result in reduced pumping capacity

Ref: Burkhoff D. Weschsler AS. Surgical ventricular remodeling: a balancing act on systolic and diastolic properties. J Thorac Cardiovasc Sug 2006; 132;459-463.

Theoretical Pressure Volume Relationships After Surgical Reverse Remodeling



Is there a corollary with ventricular volume reduction surgery?

- What is the effect of LV mass resection in failing left ventricles?
 - ◆ Resection of dyskinetic LV mass
 - ◆ Reduction in LV chamber size
 - ◆ Left shift of relationship between total ventricular work and end diastolic pressure
 - ◆ Resection of akinetic LV mass
 - ◆ Reduction in LV chamber size
 - ◆ No change in relationship of total ventricular work and EDP
 - ◆ Resection of hypokinetic LV mass
 - ◆ Reduction in LV chamber size
 - ◆ Downward shift of relationship between total ventricular work and end diastolic pressure

Ref: Artrip, Oz and Burkhoff. Left ventricular volume reduction surgery for HF: A physiologic perspective. Journal of Thoracic and Cardiovascular Surgery. 122. 2001

Important Questions that Impacted the Advisory Panel in June 2005

- Do the data support a composite endpoint?
 - ◆ Mortality effect was not significant
 - ◆ Functional status had a high degree of missing data; poor correlation between site assessed and core lab NYHA data and hopeless ambiguity in statistical interpretation; no signal in stress testing
 - ◆ Freedom from other cardiac procedures which included CRT
- This is an unblinded trial; how do you account for bias, particularly in the referral for major cardiac procedures?
- Was there sufficient evidence to support a true reverse remodeling effect?, i.e., a change in LV size and an increase in LVEF? A favorable change in BNP?

If approved, how would the previous panel or this panel write a label?

- Do we know the patient phenotype that best responds?
- Are we able to say this technology saves lives?
- Has a demonstrably favorable influence on NYHA status been proved sufficient to include such a statement in the label?
- Which cardiac procedures are most impacted? CRT? Is it preferable [or logical] to proceed with the CorCap[®] to avoid the need for CRT? Is the indication for transplantation really impacted by the CorCap[®] or the referral for transplantation?

Conclusion

- Premise - Multiple other treatment options exist with less morbidity/mortality risks.
- Hypothesis - A surgically reconfigured smaller ventricle has not yet been demonstrated by any procedure to result in similar benefits as seen with medical therapy and may actually have an adverse effect on diastolic function.
- Data - Given the amount of missing data, the need for an imputational analysis, lack of consistency in the primary and secondary objectives, there is reasonable doubt these data represent proof of concept.
- Direction – A good idea but in need of more research in a more targeted patient population

ODE Comment and Recommendation

Aron Yustein, M.D.

Deputy Director, Clinical
Office of Device Evaluation
Center for Devices and Radiological
Health

The Process

- Extensive interaction between sponsor and FDA
- Sponsor has worked diligently to provide available data and expert analysis
- ODE's goal is to protect public health, speed innovations in medical technology, and provide the public with accurate, science-based information
- FDA has reviewed all of the data presented fairly and objectively
- ODE has applied considerable resources and expertise, both internal and external, to multiple reviews

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Recommendation

- Sponsor has not provided reasonable assurance based on valid scientific evidence that the CorCap is safe and effective for its intended use
- ODE recommends that the Acorn CorCap CSD be determined Not Approvable at this time
- ODE welcomes the opportunity to work with Acorn to design an additional premarket confirmatory trial

Back-up Slides

Regulatory Timeline

Acorn Clinical Trial History

- April 2001 – FDA Disapproves Request for Pivotal Trial Expansion – **Attachment 9**
- June 2001 – Pivotal Trial Approved w/ Future Concerns – **Attachment 11**
- Sept - Nov 2001 – Discussions re: Primary Endpoint
 - ◆ 41 patients enrolled as of Oct 2001
 - ◆ **Attachments 12-14**
- Feb 2002 – Conditional Approval of Revised Protocol w/ Future Concerns – **Attachment 15**
- June 2002 – Approval of Revised Protocol (Revision 5)
 - ◆ 172 patients enrolled as of June 2002
 - ◆ Primary endpoint analysis plan includes comparison of Site NYHA at baseline to Core Lab NYHA at follow-up

Acorn Clinical Trial History

(continued)

- March 2004 – Discussion re: primary endpoint analysis plan due to high level of missing data and lack of concordance between Site and Core Lab NYHA – [Attachment 17](#)
- May 19, 2004 – FDA suggests imputation as a possible way to recover missing data – [Attachment 18](#)
- May 28, 2004 – Acorn rejects imputation, citing opinions of clinical/statistical advisors – [Attachment 19](#)
- June 1, 2004 – Acorn unblinded to study results – [Attachment 20](#)
- July 2004 – FDA advises Acorn to analyze primary endpoint according to as many methods as they believe appropriate; all analyses will be considered under the PMA – [Attachment 21](#)
- Aug 2004 – Acorn reverses stance on imputation – [Attachment 22](#)

Acorn PMA Application History

- June 22, 2005 – Circulatory System Devices Advisory Panel Meeting
 - ◆ Panel voted 9-4 in favor of Not Approvable
 - ◆ **Attachments 1-5**
- July 2005 – Discussion between FDA and Acorn re: how to move forward
 - ◆ Acorn proposes post hoc reanalysis of 300-patient cohort in attempt to address FDA and panel concerns
- August 12, 2005 – FDA issues Not Approvable Letter
 - ◆ FDA concurs with recommendation of Advisory Panel
 - ◆ Outstanding safety and effectiveness concerns
 - ◆ Options for addressing deficiencies, including concerns with *post hoc* analyses
 - ◆ **Attachment 26**

Not Approvable Letter (Option A)

Re-analyze the current data set using retrospective *post hoc* analyses that exclude high risk patients to establish a patient population in which the device is reasonably safe and effective. FDA has reviewed the information presented at a meeting held on July 19, 2005, and acknowledges that is the method that Acorn prefers. However, FDA still remains concerned about the amount of missing data. Also, while the further exclusion of high risk patients may limit some of the acute risk associated with the device, FDA remains concerned that you will be unable to demonstrate a meaningful benefit from the device in these patients.

Not Approvable Letter (Option B)

Re-analyze the current data set coupled with data collected during various OUS studies to establish a patient population in which the device is reasonably safe and effective. As indicated by Acorn during the July 19, 2005 meeting, the patient populations in the US and OUS studies are probably too diverse to allow pooling of the data. In addition, FDA also has concerns that different approaches to heart failure were used in the various studies, making it unlikely that the data would be poolable. FDA's concerns discussed in option A above are applicable to this approach as well.

Not Approvable Letter (Option C)

Re-analyze the current data set as well as the data collected during various OUS studies to establish a predicted patient population that will experience the greatest risk-benefit ratio from this device. Acorn could then conduct an additional prospective study in this specific population, using historical controls from the existing data, to obtain a data set that demonstrates reasonable safety and effectiveness.

Acorn PMA Application History (continued)

- October 25, 2005 – Acorn submits Amendment 5, including the Focused Cohort Analysis
- February 2, 2006 – Not Approvable Letter
 - ◆ Focused Cohort Analysis is *post hoc*
 - ◆ No new patient data provided since Advisory Panel
 - ◆ Additional clinical data required to prospectively validate these findings
 - ◆ **Attachment 28**

Safety of Reoperations

Re-Operations in CorCap Patients

Adhesions Reported in 7/8 Cases

- "...There were intense adhesions to the Gortex membrane which prevented adequate dissection. The RV and innominate vein were entered during dissection. The pericardium was obliterated laterally from previous operations...The Acorn wrap was especially adherent. Dissection of the heart from the pericardium was finally complete..."
- "...The heart and great vessels were encased in some of the most dense mediastinal adhesions I have encountered. In particular the Acorn sock was firmly adherent to the pericardium, as well as to the epicardium. There were almost no tissue planes between the Acorn sock and any of the surrounding structures. I left portions of the left ventricle on the inside of the pericardium on the left side to avoid injury to the phrenic nerve. There was also extensive adhesions even up to the area of the great vessels and right side of the heart..."
- "...At this point, we were unable to free up the left lateral wall or left anterior wall of the heart due to the adhesions and thick fibrotic reaction to the Acorn device in the pericardium...While on pump, we continued dissection on the left lateral wall of the heart until we were able to free up the whole left ventricle..."

Re-Operations in CorCap Patients

Adhesions Reported in 7/8 Cases

- "...adhesions of the jacket to the pericardium were extremely dense and required over an hour of meticulous difficult dissection...At times the jacket was left on the pericardium in order not to hurt the phrenic nerves..."
- "...There were extensive dense adhesions involved in the mediastinal structure from previous Acorn procedure...We noted and identified the Acorn device, which appears to be a mesh material adhering to the epicardial surface of the heart. There was an adhesion formed densely between the Acorn device and the epicardial layer of the heart. There [were] also adhesions formed densely between the Acorn material and the pericardial sac on the left side. We made very slow progress in dissecting out the Acorn device from the pericardium and the left side of the pleural space...Further dissection was then carried to free up the adhesions around the heart with bypass support. Due to the dense adhesions formed between the Acorn device and the lateral wall of the pericardium, in order to avoid injury to the left phrenic nerve, we decided to leave the Acorn mesh in place with the attachment to the lateral pericardial wall. We made a subepicardial dissection to peel the epicardial layer off the myocardial fibers. We left a piece of 10x15 cm epicardial layer and the Acorn inside the pericardial sac..."

Text taken from Operative Reports in Attachment 6

Re-Operations in CorCap Patients

Adhesions Reported in 7/8 Cases

- "...This was a very complex case that required much more time than usual...The adhesions in the chest were extremely dense, adherent, and exuberant. Identifying the pericardium and developing a plane around the heart was impossible...The left side of the pericardium was inadvertently detached from the diaphragm and the inferior aspect of the diaphragm had to be reconstructed...the recipient cardiectomy was performed with great difficulty..."
- "...The sternum was divided with some difficulty due to dense, fixed adhesions posteriorly...Then began a very intense and difficult dissection for a period of approximately two hours to obtain mobilization of the heart and gain good access for CPB. The Acorn device had produced severe, dense adhesions throughout the mediastinum, and the procedure for freeing the heart was extremely tedious and long...Dissecting the heart continued to be difficult and we had to essentially do it piecemeal...The adhesions around the pulmonary artery and the left atrium were particularly difficult to deal with, but we eventually were able to excise the heart in order to perform the transplant..."

Re-Operations in Control Patients

Adhesions Reported in 12/22 Cases

- "...The heart was dissected free of mediastinal adhesions, and the patient underwent standard bicaval cannulation..."
- "...There was evidence of dense pericardial adhesions..."
- "...Mediastinal and intrapericardial adhesions were carefully lysed..."
- "...With great difficulty, the very thick adhesions between the heart and the mediastinum were divided with blunt and sharp dissection..."
- "...The sternum was then opened, and dense adhesions were taken down, exposing the ascending aorta, the right atrium, and anterior left ventricle..."
- "...Adhesions to the heart were actually quite severe but were taken down without difficulty..."

Re-Operations in Control Patients

Adhesions Reported in 12/22 Cases

- "...Dissection was again performed with lysis of adhesions, which were quite severe given her multiple previous heart surgeries. The dissection was rather time consuming, taking approximately one hours time...Adhesions were extremely dense over the great vessels..."
- "...Multiple dense adhesions were lysed..."
- "...The patient's [adhesions] were moderate in nature and we were able to identify the right atrium and ascending aorta without difficulty..."
- "...The pericardial adhesions were lysed. We were able to gain exposure to the right atrium and ascending aorta..."
- "...Adhesions were dissected..."
- "...There were dense adhesions in the mediastinum which required some time for dissection..."

Text taken from Operative Reports in Attachment 7

Results Analyzed by Strata

Primary Endpoint Analyzed by Strata

Analysis Description	# Pts	Odds Ratio (95% CI)	p-value
No MVR	107	2.57 (1.09, 6.08)	0.032
MVR	193	1.51 (0.84, 2.72)	0.17
All Patients	300	1.73 (1.07, 2.79)	0.024

Table 8 from Executive Summary

Components of Primary Endpoint Analyzed by Strata

Component	Odds/Hazard Ratio (T/C)	p-value
No MVR Stratum		
Mortality	Not Provided	0.71
Major Cardiac Procedures	0.28	0.02
Core Lab NYHA [*]	2.37	0.16
MVR Stratum		
Mortality	Not Provided	1.0
Major Cardiac Procedures	0.57	0.11
Core Lab NYHA [*]	1.45	0.35
All Patients		
Mortality	Not Provided	0.83
Major Cardiac Procedures	0.46	0.009
Core Lab NYHA [*]	1.64	0.12

Table 9 from Executive Summary

Secondary Endpoints by Strata

Endpoints	Treatment Difference (T-C)		
	All Patients	No MVR	MVR
Cardiac Structural			
LVEDV (ml)	-17.89	-22.24	-14.81
LVESV (ml)	-15.23	-19.96	-14.12
LVEF (%)	0.83	-0.9*	1.95
Sphericity Index	0.04	0.0002	0.07
LV Mass Index (g/m ²)	-5.9	-6.22	-6.3
LVEDD (mm)	-1.8	-0.64	-2.35
LVESD (mm)	-1.2	-0.42	-1.53
Patient Functional			
MLHF	-4.47	-4.76	-4.22
Site NYHA	-0.04	-0.29	0.10*
6MW (m)	-21.9*	N/A	N/A
Peak VO ₂ (ml/kg/min)	-0.62*	N/A	N/A
SF-36 General Health	9.13	5.28	10.39
SF-36 Physical Function	5.41	5.9	5.16
Other			
BNP (pg/ml)	77.33*	93.60*	70.26*

* Favors Control

Table 10 from Executive Summary

Focused Cohort

- Post hoc analysis
- Needs to be prospectively tested
- History of other HF trials with pharmacotherapy
 - ◆ Initial findings with subgroup post hoc analysis
 - ◆ Disproved in subsequent prospective testing

PRAISE 2 Study Results

	PRAISE 2		PRAISE 1 and 2	
	Amlodipine	Placebo	Amlodipine	Placebo
Patients	826	826	1408	1397
Deaths	262*	278	479†	466
Mortality	31.7%	33.6%	34.0%	33.4%

*Odds ratio = 1.09 (p=0.28)

†Odds ratio = 0.98

No differences were seen in different subgroups of the study population (age, sex, NYHA class, ejection fraction).

ELITE I

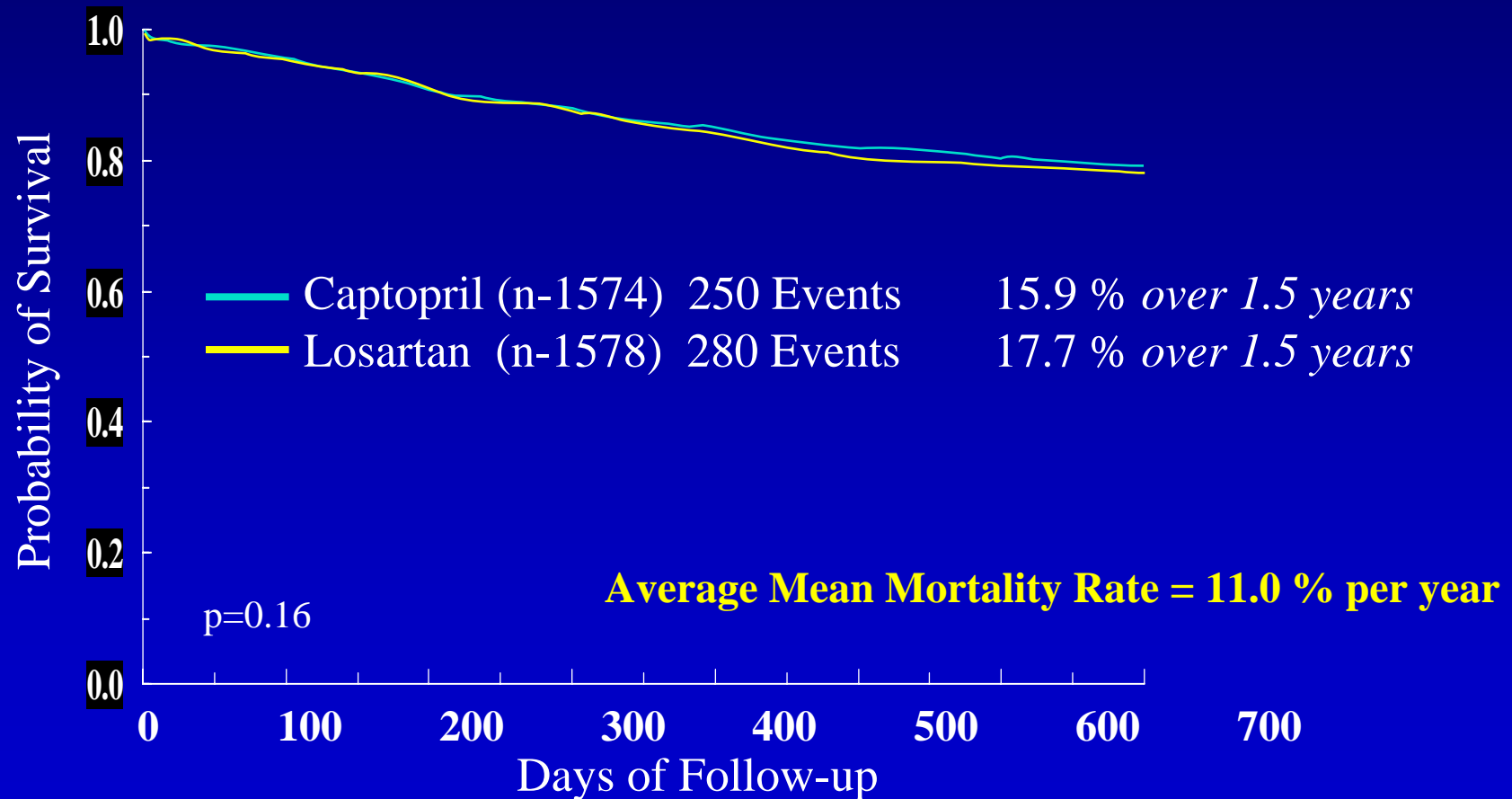
Evaluation of Losartan in the Elderly

	Losartan (n=352)	Captopril (n=370)	p value
Increase in serum creatinine	10.5%	10.5%	
Discontinuation of therapy because of side effects	12.2%	20.8%	0.002
Death and/or hospital admission for heart failure	9.4%	13.2%	0.075
All-cause mortality	4.8%	8.7%	0.035

Treatment with losartan was associated with an unexpected lower mortality than treatment with captopril.

ELITE II

Primary Endpoint: All-Cause Mortality



Pitt, B. et al, Lancet 2000; 355:1582-87

Reverse Remodeling Hypothesis

Majority of Change in LV Mass Attributable to MVR

