

# Summary of the CorCap CSD Clinical Study

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# Study Design

- 300-patient randomized, prospective, controlled, multi-center trial
  - Stratified into MVR, no-MVR by clinical judgment
- 29 sites in the US and Canada
  - Randomized to CorCap/no CorCap within site and within MVR and no-MVR strata
- All patients received optimal medical therapy
- Intent-to-treat analysis for primary endpoint
- Data Analysis Plan pre-specified pooling of strata and reporting as one cohort
- Functional status evaluated at 3, 6, 12, and every 6 months until common closing date of July 4, 2004

# CorCap Trial Inclusion/Exclusion

## Inclusion Criteria

- Men and women age 18-80 years of age
- NYHA class III – IV HF\* of ischemic or non-ischemic etiology
- LVEF  $\leq$  35%\* and LVEDD  $\geq$  60 mm
- 6 minute walk test < 450 meters
- Stable optimal medical therapy

## Exclusion Criteria

- Patent CABG
- On active transplant list
- Criteria for patients who are too sick

\*In MVR stratum: NYHA class II and/or EF < 45% was allowed

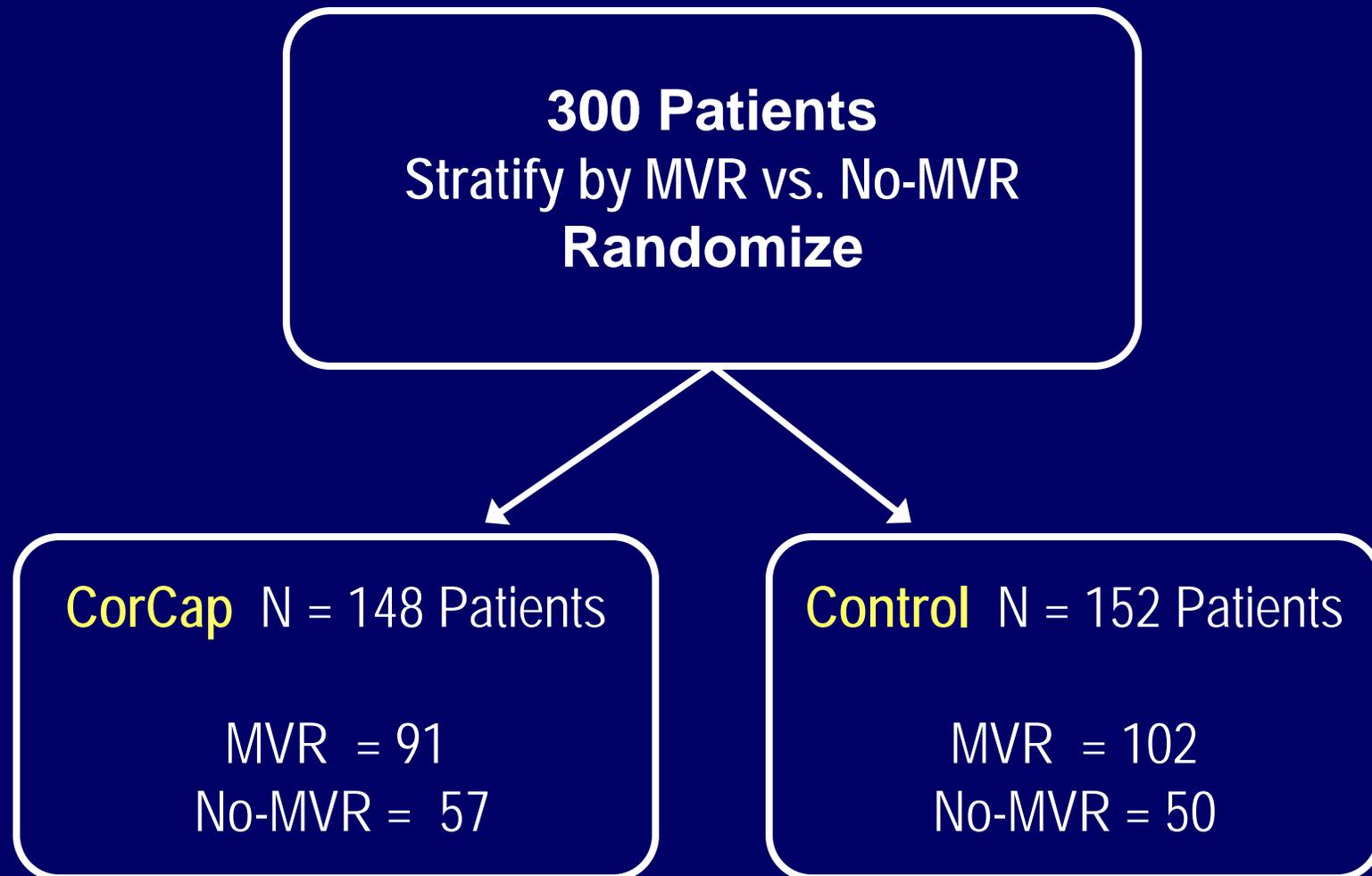
# Primary Composite Endpoint – Patient Status at End of Study

Outcome Measure	Improved	Same	Worsened
Mortality	Alive <i>and</i>	Alive <i>and</i>	Death <i>or</i>
Major Cardiac Procedure	Did Not Have an MCP <i>and</i>	Did Not Have an MCP <i>and</i>	Had an MCP <i>or</i>
NYHA Class	Decrease (1+ Class)	No change	Increase (1+ Class)

# Rationale for Composite Endpoint

- 3 clinically meaningful components
  - Mortality
  - Blinded NYHA
  - MCPs
- Allow patients to have other procedures but outcomes still “count” in overall analysis
- Accounts for all ways that patients could deteriorate
- Only way for patient to “improve” is to have  $\geq 1$  class decrease in NYHA class

# CorCap Randomized Trial Patient Enrollment



# Patient Follow-Up

- Minimum follow-up: 12 months
- Median follow-up: 23 months
- Vital status missing for 1 patient

## Test Compliance for Visits Attended: At Follow-up Intervals

Test	6 Month Visit			12 Month Visit		
	Actual	Expected	%	Actual	Expected	%
Core Lab NYHA	170	195	87%	210	220	95%
Echo	241	261	92%	229	238	96%
MLHF	250	270	93%	244	251	97%

# Primary Endpoint Results

Result	Treatment	Control	Odds Ratio 95% CI	p-value
Improved	38%	27%	1.73* (1.07, 2.79)	0.024
Same	25%	28%		
Worsened	37%	45%		

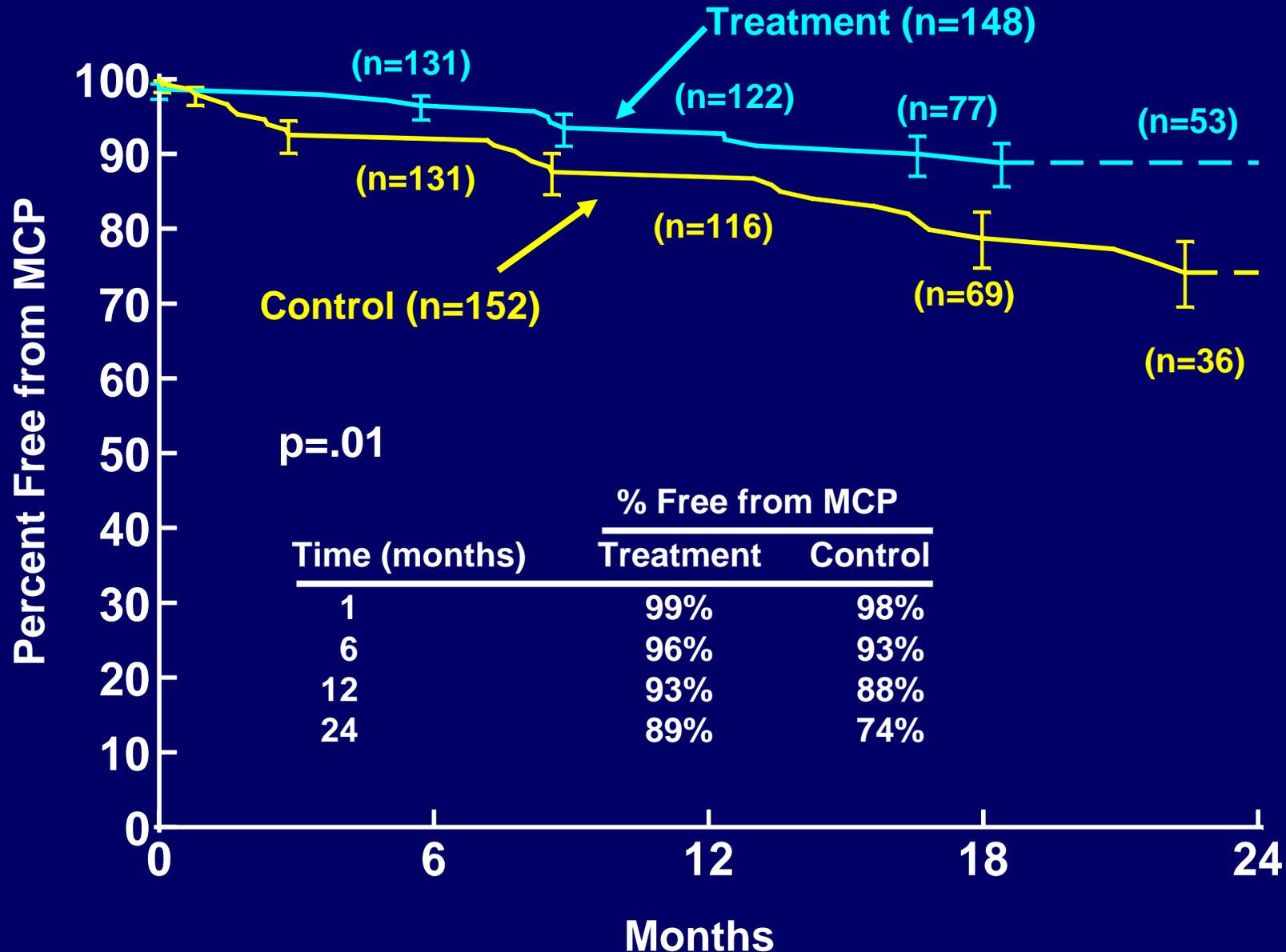
*\* Proportional odds ratio indicates treatment patients had a 73% greater odds of being in a better category than control patients*

As of common closing date (4 July 2004)  
Median Follow-up = 23 months

# Primary Endpoint Results by Stratum

	Odds Ratio	95% CI
Overall	1.73	1.07 – 2.79
MVR Stratum (n = 91/102)	1.51	0.84 – 2.72
No-MVR Stratum (n = 57/50)	2.57	1.09 – 6.08

# Freedom from Major Cardiac Procedures



# Major Cardiac Procedures

Procedure Type	Treatment	Control
	# Pts	# Pts
Cardiac Transplant	7	16
VAD	3	8
Repeat Mitral Surgery	1	3
Bi-Ventricular Pacing	10	14
Repeat Tricuspid Surgery	0	2
Any of Above	19	33

# Change In Core Lab NYHA Classification

## Per-protocol Analysis\* of Core Lab NYHA

Result	Treatment	Control	Odds Ratio
Improved	52%	43%	1.64 (0.87, 3.08)
Same	35%	43%	
Worsened	13%	14%	

\* Omits patients who died or had MCP (assesses outcome in 200 patients)

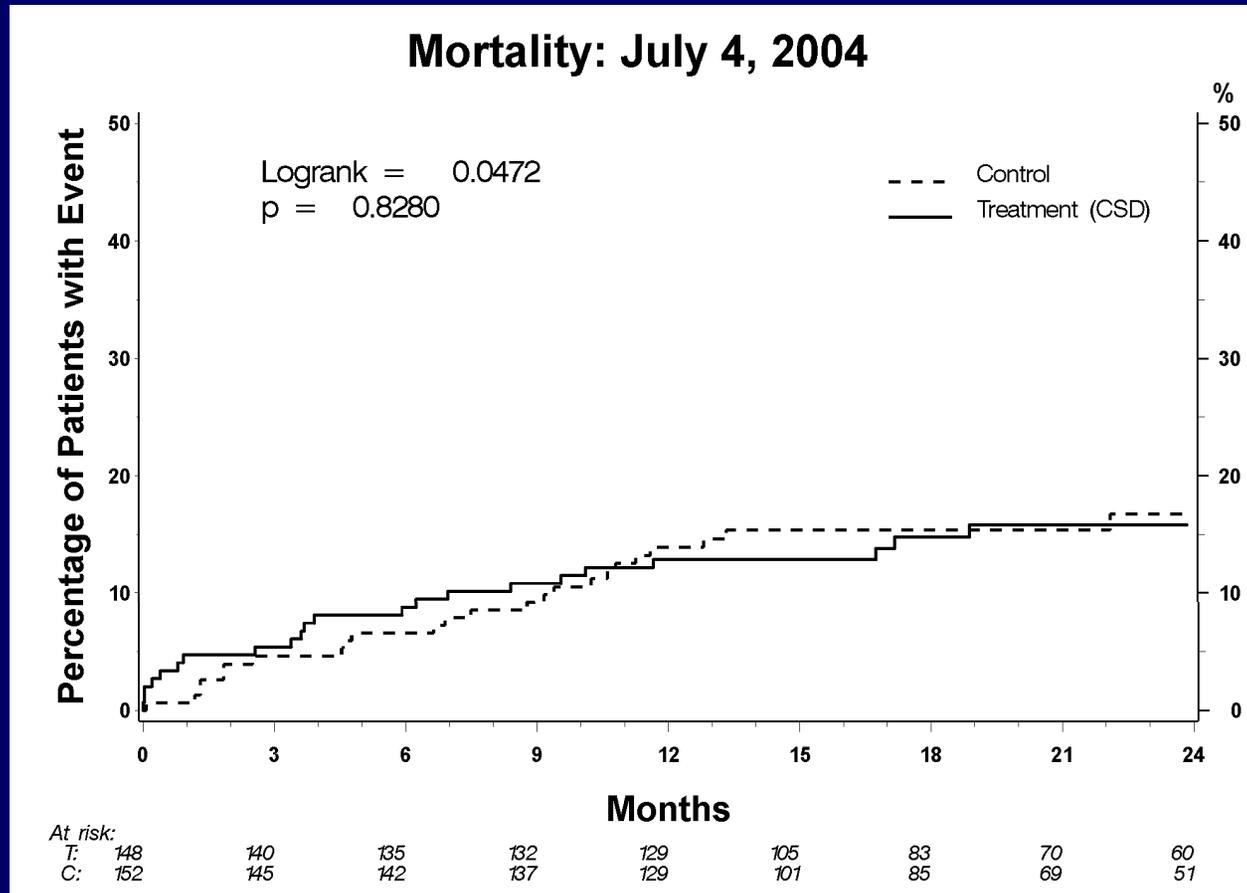
# Change In Core Lab NYHA Classification

## ITT Analysis\* of Core Lab NYHA

Result	Treatment	Control	Odds Ratio
Improved	38%	27%	1.73 (1.07, 2.79)
Same	25%	28%	
Worsened	37%	45%	

\* Classifies deaths as “Class V” and MCPs as one class worse than baseline (assesses outcome in 293 patients)

# Mortality – Through July 2004



# Serious Adverse Events (> 5% Incidence)

July 2004

Adverse Event	CorCap (n=148)		Control (n=152)		p-value
	# Patients	%	# Patients	%	
Arrhythmia	48	32.4	58	38.2	0.39
Bleeding	9	6.1	14	9.2	0.33
Hemodynamic Compromise	83	56.1	73	48.0	0.18
Infection/Pneumonia	46	31.1	35	23.0	0.08
Neurological Deficit/Stroke	16	10.8	11	7.2	0.23
Pulmonary Compromise	29	19.6	22	14.5	0.17
Renal Compromise	15	10.1	8	5.3	0.12
Other	59	39.9	58	38.2	0.74
Any SAE	120	81.1	118	77.6	0.43

# Serious Adverse Events (> 5% Incidence)

April 2005

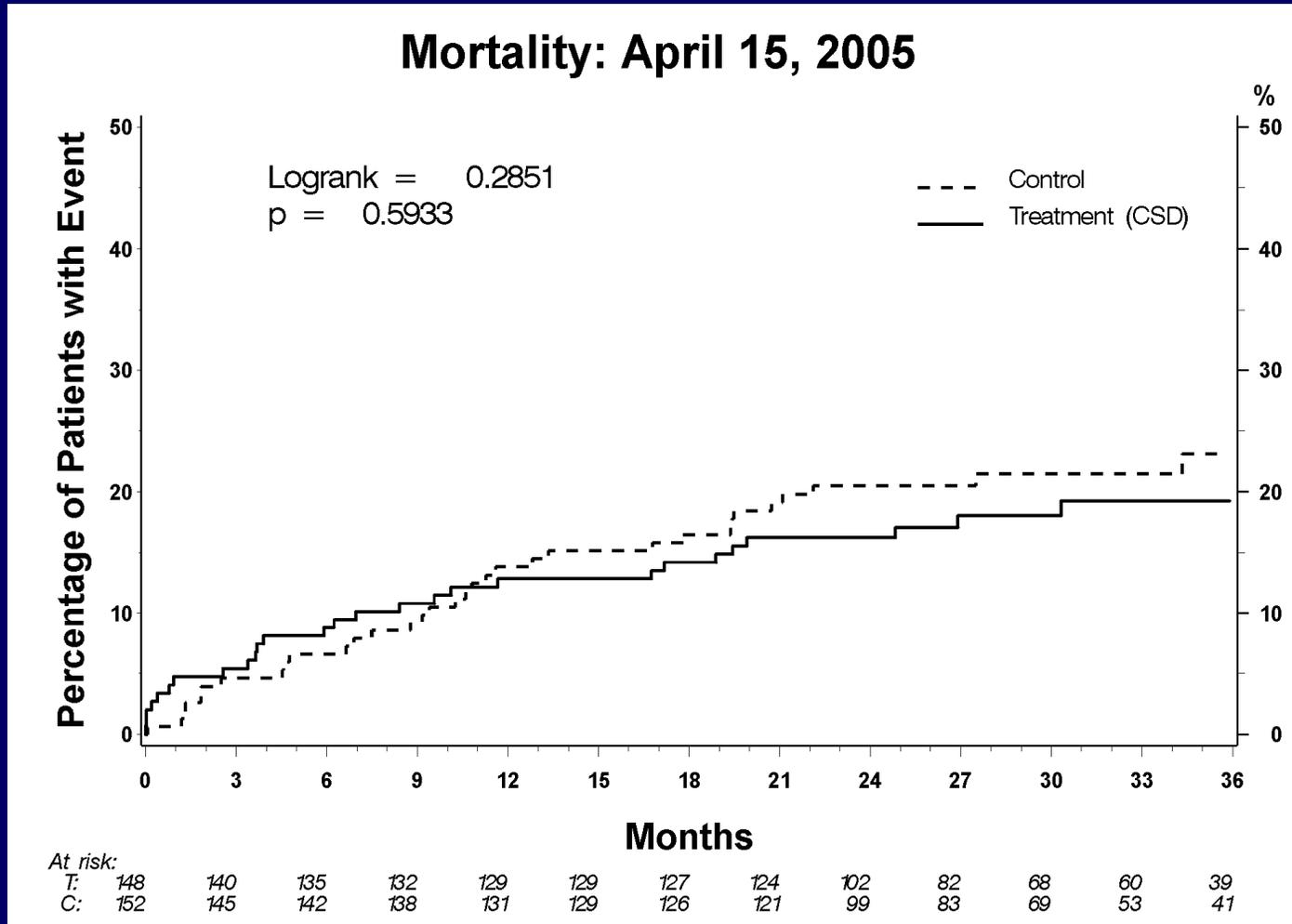
Adverse Event	CorCap (n=148)		Control (n=152)		p-value
	# Patients	%	# Patients	%	
Arrhythmia	51	34.5	60	39.5	0.46
Bleeding	9	6.1	15	9.9	0.23
Hemodynamic Compromise	90	60.8	74	48.7	0.04
Infection/Pneumonia	47	31.8	37	24.3	0.11
Neurological Deficit/Stroke	16	10.8	12	7.9	0.34
Pulmonary Compromise	31	20.9	23	15.1	0.14
Renal Compromise	17	11.5	8	5.3	0.052
Other	63	42.6	61	40.1	0.62
Any SAE	123	83.1	120	78.9	0.33

# Mortality: July 4, 2004

MVR Stratum	Treatment (n=91)	Control (n=102)
≤ 30 Days	2	1
31 days – 60 days	0	5
61 days - 12 Months	9	9
> 12 Months	4	2
Total	15	17
No MVR Stratum	Treatment (n=57)	Control (n=50)
≤ 30 Days	5*	0
31 days – 60 days	0	0
61 days - 12 Months	3	6
> 12 Months	2	2
Total	10	8

\* Includes one patient who died prior to surgery.

# April 2005 Safety Update - Mortality



# Secondary Endpoints

	Secondary Endpoints	Treatment Difference (T-C)	Individual p-value
Structural	LVEDV	-17.9ml	0.008
	LVESV	-15.2ml	0.02
	LVEF	0.83	0.49
	Sphericity Index	0.042	0.031
	Mass Index	-5.9g/m <sup>2</sup>	0.15
	LVEDD	-1.8mm	0.02
	LVESD	-1.2mm	0.21
Functional	MLHF	-4.47	0.04
	SF-36 (GH)	9.13	<0.0001
	SF-36(PF)	5.41	0.015
	NYHA (Site Assessed)	-0.04	0.60
	6-minute Walk Distance	1.27 (odds ratio)	0.24
	Peak VO <sub>2</sub>	1.37 (odds ratio)	0.15
Lab	BNP	77.33 pg/ml	0.014
Clinical	All Cause Re-Hospitalizations	1.0	0.44
	Mortality or Re-Hospitalizations	1.02 (odds ratio)	0.88

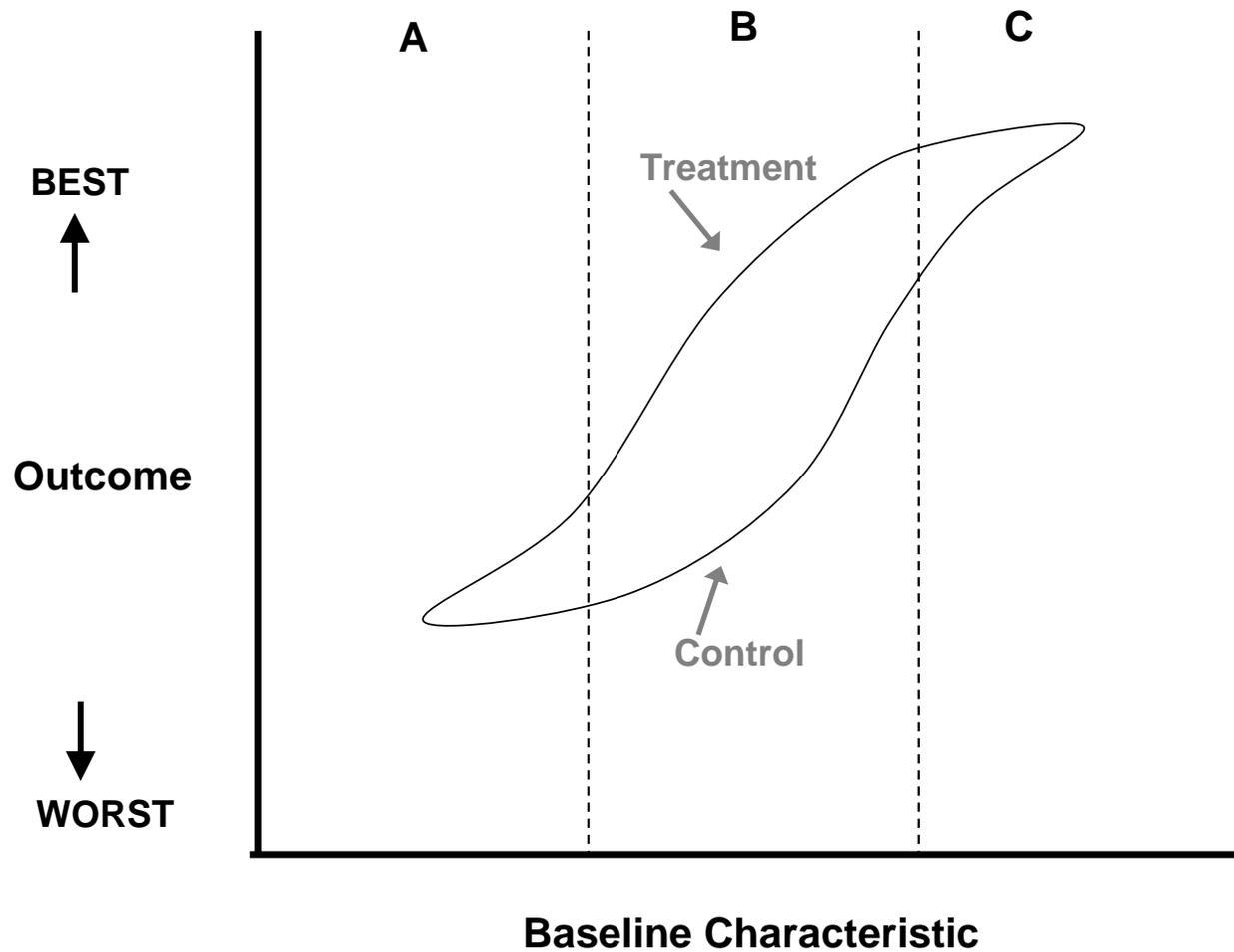
# Conclusions

- CorCap Randomized Trial achieved primary endpoint (p=0.024)
- Secondary endpoints (LVEDV, LVESV, Sphericity, MLHF, SF-36) supported primary endpoint
- Safety profile acceptable
- Provides reasonable assurance [21 CFR 860.7 (d) and (e)] of safety and efficacy

# ***Post Hoc Analyses***

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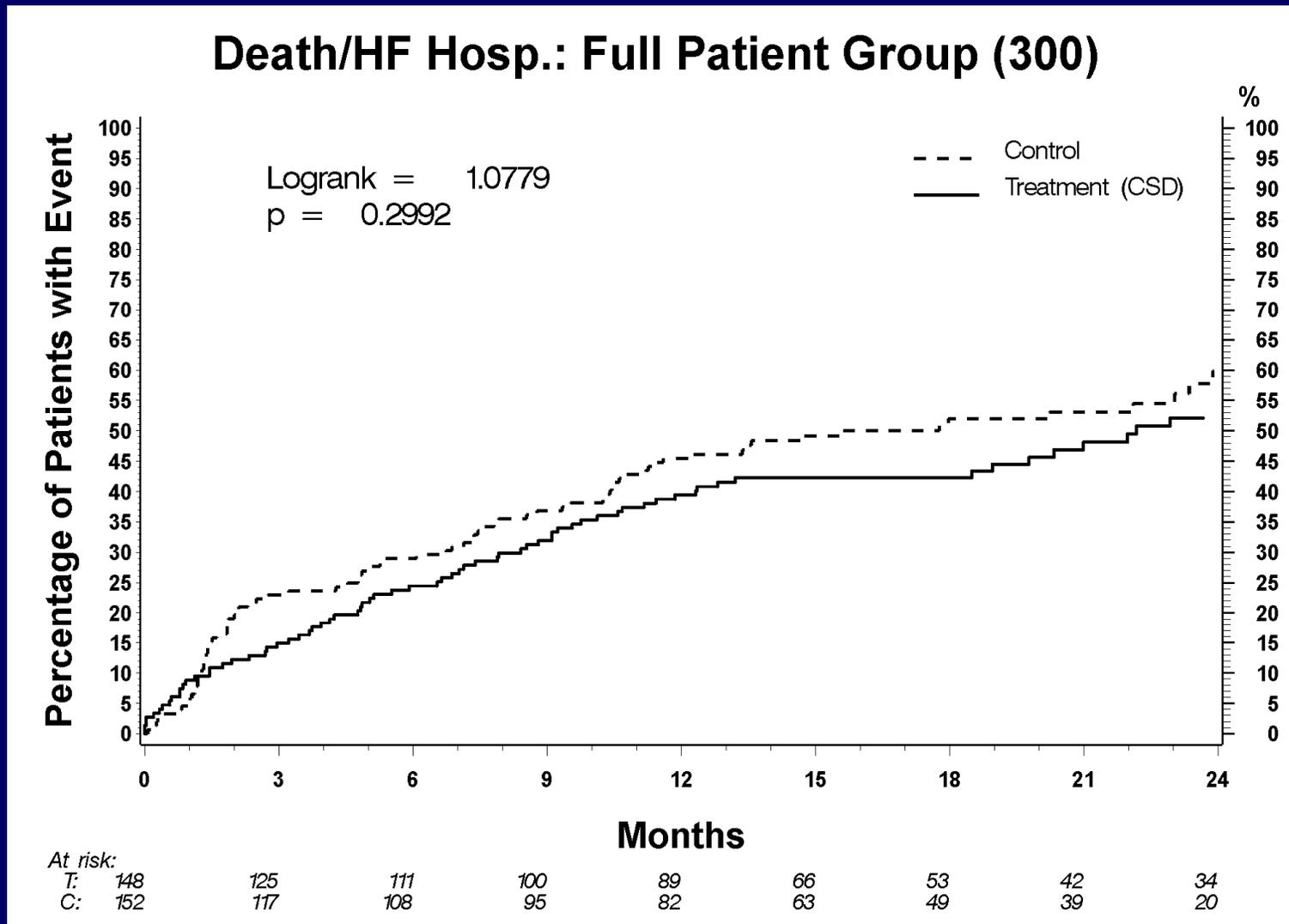
# Key Concept: How to find patients with the largest treatment effect



# Focused Cohort

- FDA suggested post-hoc exploratory analysis excluding high-risk patients
- Identify patients with best outcomes in treated relative to untreated
  - LVEDDi  $\geq 30$  mm/m<sup>2</sup> and  $\leq 40$  mm/m<sup>2</sup>
- Developed in collaboration with clinicians
- Assist in labeling and patient selection
- Identified reasonable subgroup that may derive even more benefit than full cohort
  - Improved primary endpoint (OR=2.45; p=0.011)
  - 34% reduction in mortality (p=0.17)
  - Perioperative mortality rate 1.3% (1/77), no excess surgical risk for treatment
  - Significant improvement in MCP (p=0.013)
  - Significant improvement in Death/HF related hospitalizations (p=0.04)
  - In No-MVR stratum, primary endpoint OR=8.33; p=0.006
  - Consistent benefit in secondary endpoints

# Full Cohort: Death or HF Hospitalizations



# Focused Cohort: Death or HF Hospitalizations

