

# CoreValve US Pivotal Trial Extreme Risk Iliofemoral Study Results

**Jeffrey J. Popma, MD**

On Behalf of the CoreValve US Clinical Investigators

# Conflict of Interest

Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below.

## Physician Name

## Company/Relationship

**Jeffrey J. Popma, MD**

**Research Grants: Cordis, Boston Scientific, Medtronic, Abbott, Abiomed, Covidien, eV3,**

**Medical Advisory Board: Cordis, Boston Scientific, Covidien**

# CoreValve Bioprosthesis

**Outflow  
Orientation**

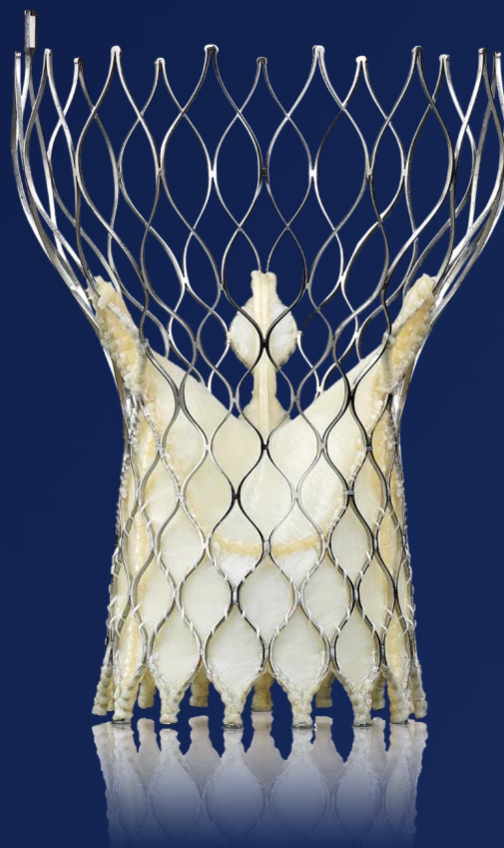
---

**Constrained Portion**

Valve Function

---

**Inflow Portion  
Sealing**



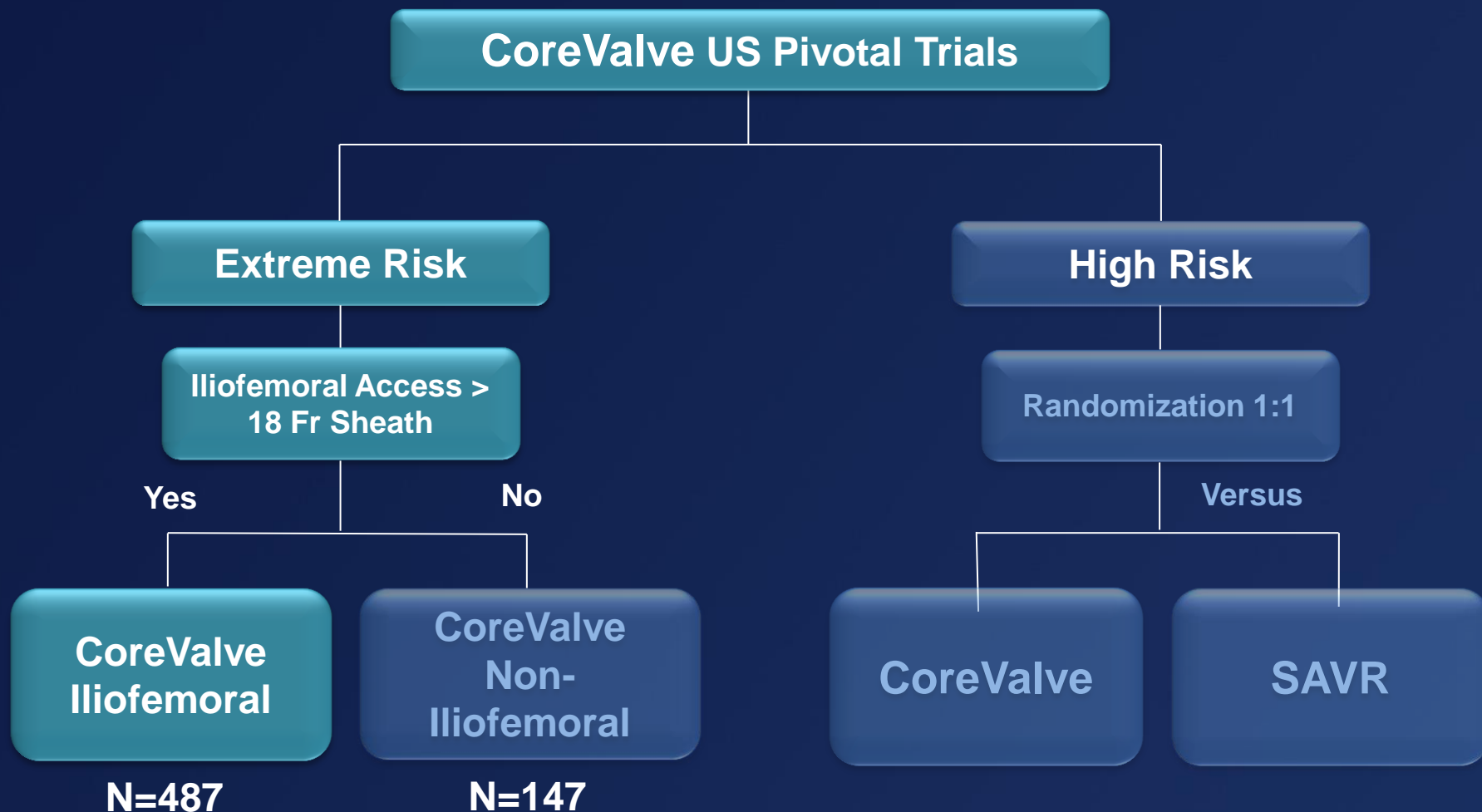
**Maximizes Flow**

---

**Supra-annular leaflet function  
Designed to avoid coronaries**

---

**Intra-annular anchoring  
Mitigates paravalvular aortic  
regurgitation**



# Study Purpose

**Study Purpose:** To evaluate the safety and efficacy of the CoreValve THV for the treatment of patients with symptomatic severe aortic stenosis in whom the predicted risk of operative mortality or serious, irreversible morbidity was 50% or greater at 30 days

**Risk Determined by:** Two Clinical Site Cardiac Surgeons and One Interventional Cardiologist

**Risk Confirmed by:** Two Screening Committee Cardiac Surgeons and One Interventional Cardiologist

**Primary Endpoint:** All Cause Mortality or Major Stroke at 12 Months

## Co-Principal Investigators

Jeffrey Popma, BIDMC, Boston

David Adams, Mt. Sinai, New York

## Steering Committee

CS's: Michael Reardon, G. Michael Deeb, Joseph Coselli, David Adams, Tom Gleason

IC's: James Hermiller, Steven Yakubov, Maurice Buchbinder, Jeffrey Popma

Consultants: Blasé Carabello, Patrick Serruys

## Data & Safety Monitoring Board

Chair: David Faxon, Brigham and Women's Hospital

## Echo Core Laboratory

Chair: Jae Oh, Mayo Clinic

## Rotational X-ray Core Laboratory

Chair: Philippe Genereux, CRF

## Clinical Events Committee

Chair: Donald Cutlip, HCRI

## ECG Core Laboratory

Chair: Peter Zimetbaum, HCRI

## Quality of Life and Cost-Effective Assessments

Chair: David J. Cohen, Mid-America Heart Institute

Matt Reynolds, HCRI

## Pathology Core Laboratory

Chair: Renu Virmani, CV Path

## Screening Committee

Chair: Michael Reardon, David Adams, John Conte, G. Michael Deeb, Tom Gleason, Jeffrey Popma, Steven Yakubov

## Sponsor

Medtronic, Inc.

# Inclusion and Exclusion Criteria

## Inclusion Criteria:

- Severe aortic stenosis:  $AVA \leq 0.8 \text{ cm}^2$  or  $AVA_I \leq 0.5 \text{ cm}^2/\text{m}^2$  AND mean gradient  $> 40 \text{ mm Hg}$  or peak velocity  $> 4 \text{ m/sec}$  at rest or with dobutamine stress (if LVEF  $< 50\%$ )
- NYHA functional class II or greater

## Exclusion Criteria (selected):

- Recent active GI bleed (3 mos), stroke (6 mos), or MI (30 days)
- Creatinine clearance  $< 20 \text{ mL/min}$
- Significant untreated coronary artery disease
- LVEF  $< 20\%$
- Life expectancy  $< 1 \text{ year}$  due to co-morbidities

# Screening Committee

- Chairman: Mike Reardon, MD
- Twice weekly phone call with a minimum of 2 Cardiac Surgeons and 1 Interventional Cardiologist
- Executive Summary to expedite review and document:
  - STS PROM and incremental factors reviewed
  - Independent review of transthoracic echocardiogram
  - Independent review of chest/abdominal CTA findings
  - Planned access route by clinical team
- Case by case telephone discussion with Heart Team



# Objective Performance Goal

- An objective performance goal (OPG) was used to estimate the risk of all-cause mortality or major stroke in patients treated with standard therapy
- OPG constructed from:
  - Meta-analysis of 5 contemporary balloon valvuloplasty series → random effects meta-analytic all-cause mortality or major stroke rate at 12 months = 42.7% (95% CI 34.0%-51.4%)
  - 12-Month PARTNER B all-cause mortality or major stroke rate of 50.3% with a corresponding 95% lower confidence bound of 43.0%

# Sample Size Determination

**Hypothesis:** TAVR with the CoreValve System is superior to standard therapy using an OPG of 12 month rate of all-cause mortality or major stroke:

$$H_0: \pi_{\text{MCS TAVR}} \geq 43\%$$

$$H_A: \pi_{\text{MCS TAVR}} < 43\%$$

**Sample Size Determination:** 438 patients

One sided alpha = 0.025

$$\pi_0 = 43\%$$

Power = 80%

$$\pi_{\text{TAVR}} = 36.5\%$$

**Study Size:** 487 patients to account for up to 10% drop out rate

# Analysis Cohort

- Primary Analysis was performed using the “As-Treated” population: all enrolled iliofemoral subjects with a documented attempt for an iliofemoral implant procedure – defined when subject was brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed

# Participating Sites



487 Patients Enrolled at 40 Participating Sites

# 16 Clinical Sites Enrolled $\geq 15$ Patients

## Methodist DeBakey Heart & Vascular

Houston, TX

Neil Kleiman, Michael Reardon

## St. Vincent Heart Center of Indiana

Indianapolis, IN

David Heimansohn, James Hermiller

## Duke University Medical Center

Durham, NC

Kevin Harrison, Chad Hughes

## Saint Luke's Episcopal Hospital

Houston, TX

Joseph Coselli, Jose Diez

## Detroit Medical Center

Detroit, MI

Ali Kafi, Theodore Schreiber

## Banner Good Samaritan

Phoenix, AZ

Tim Byrne, Michael Caskey

## Riverside Methodist Hospital

Columbus, OH

Daniel Watson, Steven Yakubov

## Vanderbilt Medical Center

Nashville, TN

John Byrne, David Zhao

34

27

27

25

23

21

21

20

## University of Kansas Hospital

Kansas City, KS

Peter Tadros, George Zorn

## Aurora St. Luke's Medical Center

Milwaukee, WI

Tanvir Bajwa, Daniel O'Hair

## Mount Sinai Medical Center

New York, NY

David Adams, Samin Sharma

## University of Miami Health System

Miami, FL

Eduardo de Marchena, Tomas Salerno

## Beth Israel Deaconess Medical Center

Boston, MA

Kamal Khabbaz, Jeffrey J. Popma

## Geisinger Medical Center

Danville, PA

Alfred Casale, Kim Skelding

## University of Michigan Health Systems

Ann Arbor, MI

G. Michael Deeb, Stan Chetcuti

## St. Francis Hospital

Roslyn, NY

George Petrossian, Newell Robinson

20

18

17

16

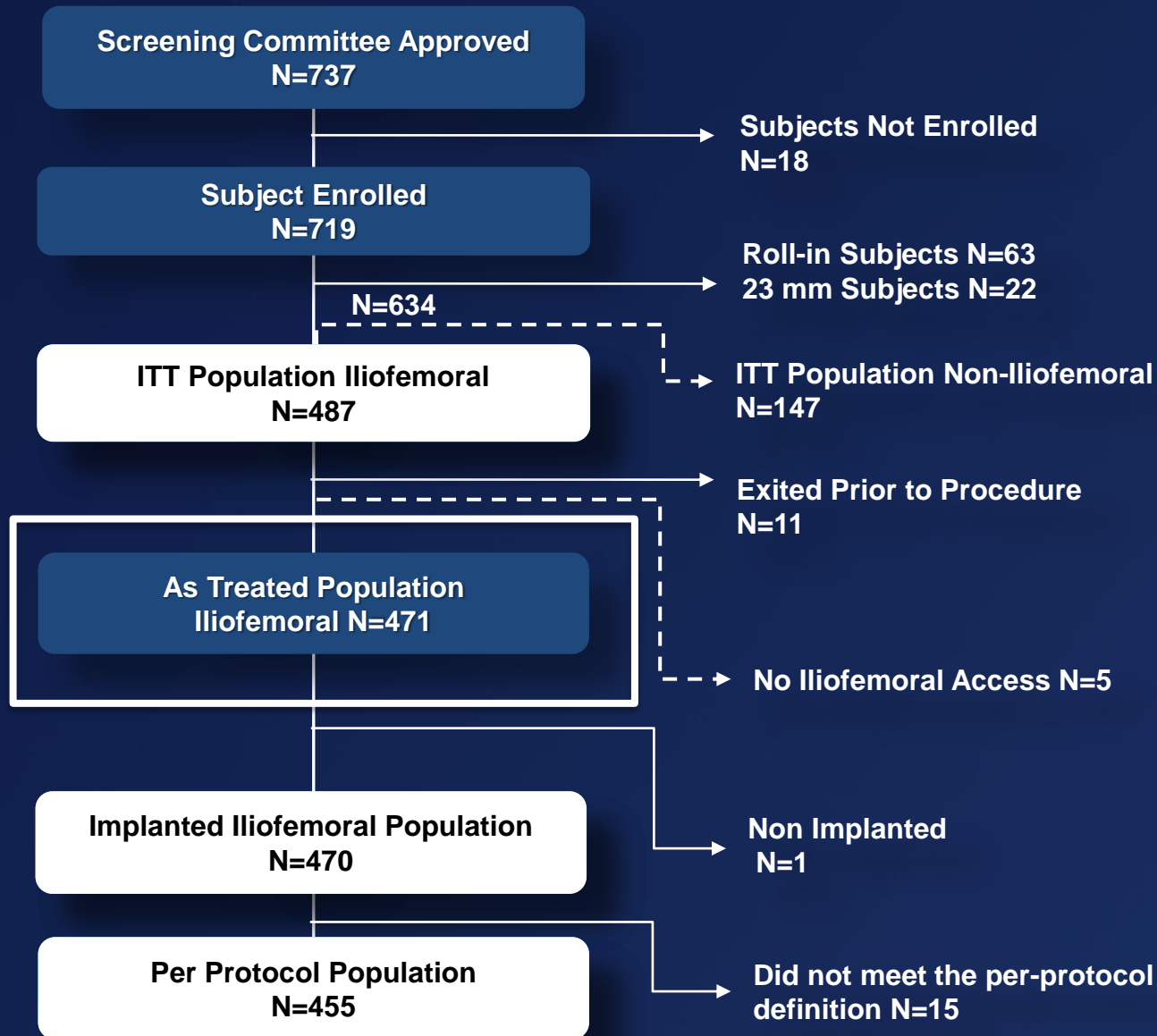
16

16

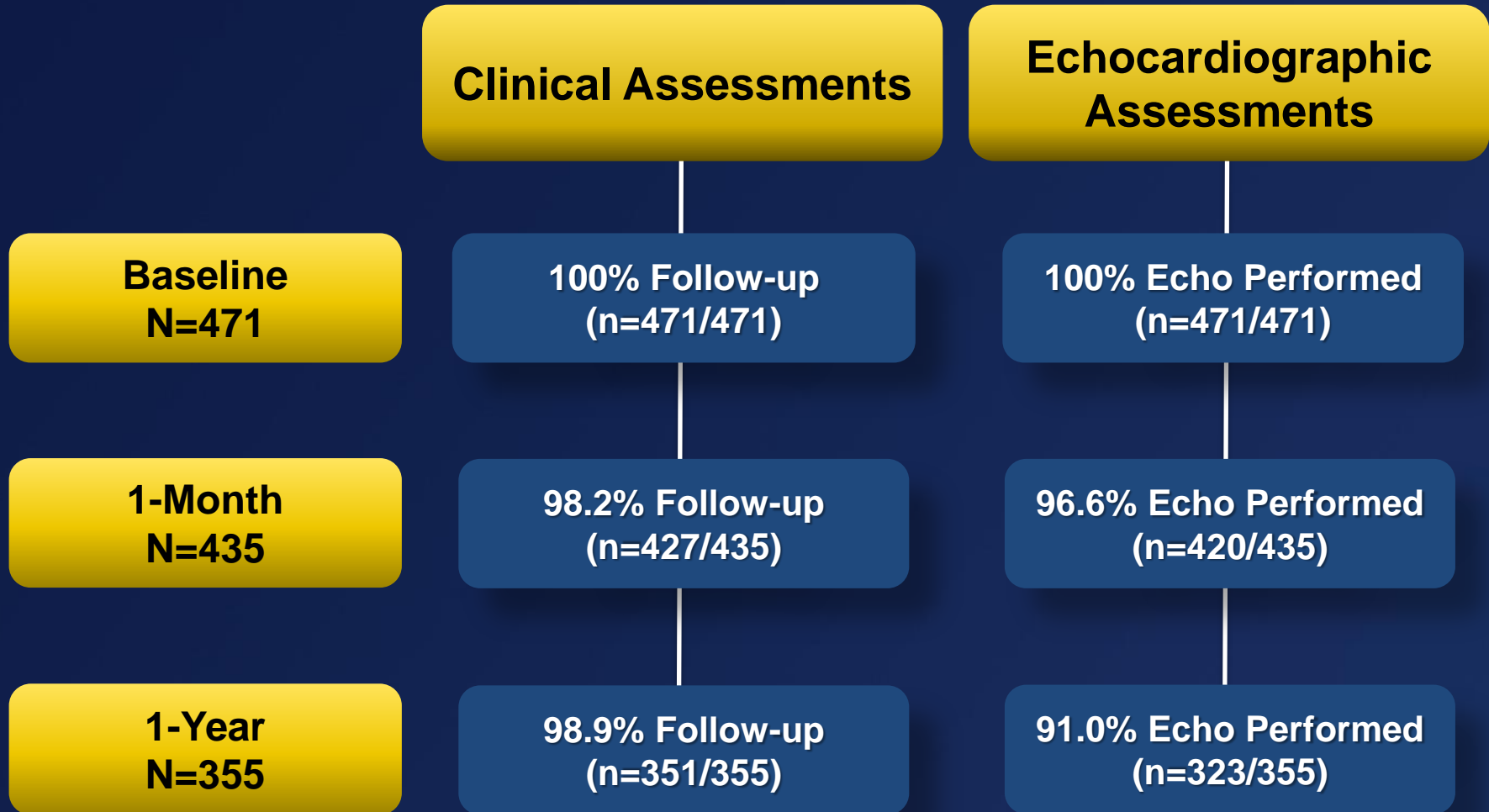
15

15

# Study Disposition



# Study Compliance



# Baseline Demographics

Characteristic	N=471
Age, years	83.1 ± 8.6
Men, %	49.0
STS Predicted Risk of Mortality, %	10.3 ± 5.6
Logistic EuroSCORE, %	22.7 ± 17.4
New York Heart Association (NYHA)	
NYHA Class III/IV, %	91.9
Diabetes Mellitus, %	42.5
Insulin Requiring Diabetes, %	19.1
Prior Stroke, %	13.8
Modified Rankin 0 or 1, %	71.9
Modified Rankin > 1, %	28.1



# Prohibitive Chest Anatomy

Characteristic	N=471
Any Anatomic Characteristic, %	31.7
Aorta Calcification*, %	
Severe, %	17.2
Porcelain, %	4.9
Hostile Mediastinum, %	11.5
Chest Wall Deformity, %	5.1

\*Aorta calcification is measured on screening CT angiogram

# Baseline Co-Morbidities

Co-Morbidity Assessment	N=471
Any Chronic Lung Disease (STS Criteria), %	58.8
Moderate, %	15.3
Severe*, %	24.0
Home Oxygen, %	30.4
FEV1 ≤ 1000 cc, %	23.1
Diffusion Capacity < 50%, %	22.3
Charlson Co-Morbidity Score**, %	5.3 ± 2.3
Moderate (3, 4), %	32.9
Severe (≥ 5), %	58.6

\*STS Criteria: Severe = FEV1 < 50% predicted and/or RA pO<sub>2</sub> < 60 or pCO<sub>2</sub> > 50

\*\*Charlson Score: = 1 MI, CHF, PVD, CVD, dementia, chronic lung disease, connective tissue disease, ulcer, mild liver disease, DM; = 2 hemiplegia, mod-severe kidney disease, diabetes with end organ damage, leukemia, lymphoma; = 3 moderate or severe liver disease; = 6 metastatic solid tumor, AIDS

# Frailty Assessment

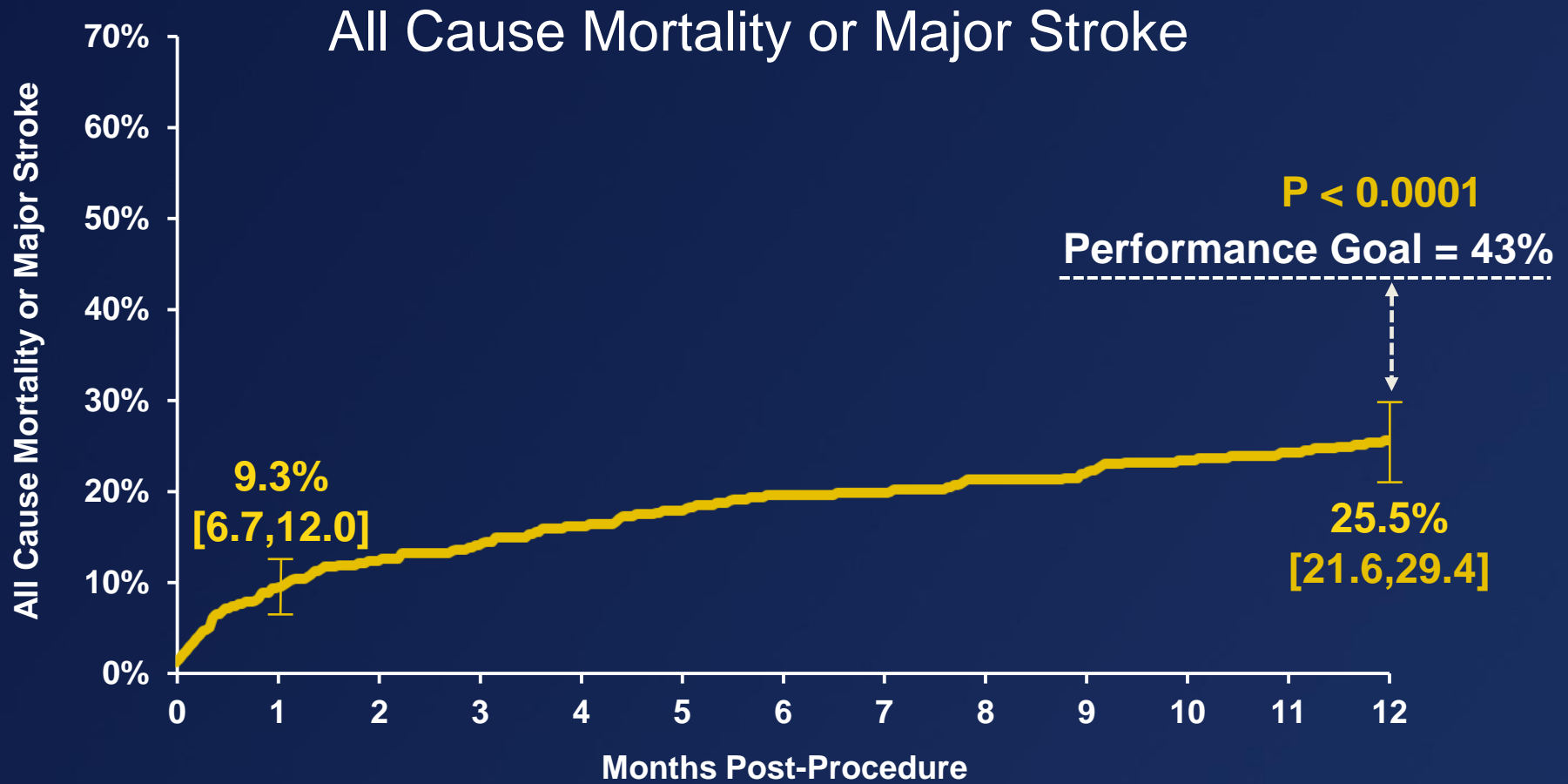
Frailty Characteristic	N=471
Anemia With Prior Transfusion, %	22.9
BMI < 21 kg/m <sup>2</sup> , %	7.6
Albumin < 3.3 g/dL, %	18.5
Unplanned Weight Loss > 10 pounds, %	16.9
Falls in Past 6 Months, %	17.8
5 Meter Gait Speed > 6 secs, %	84.2
Grip Strength < Threshold, %	67.6

# Disability Assessment

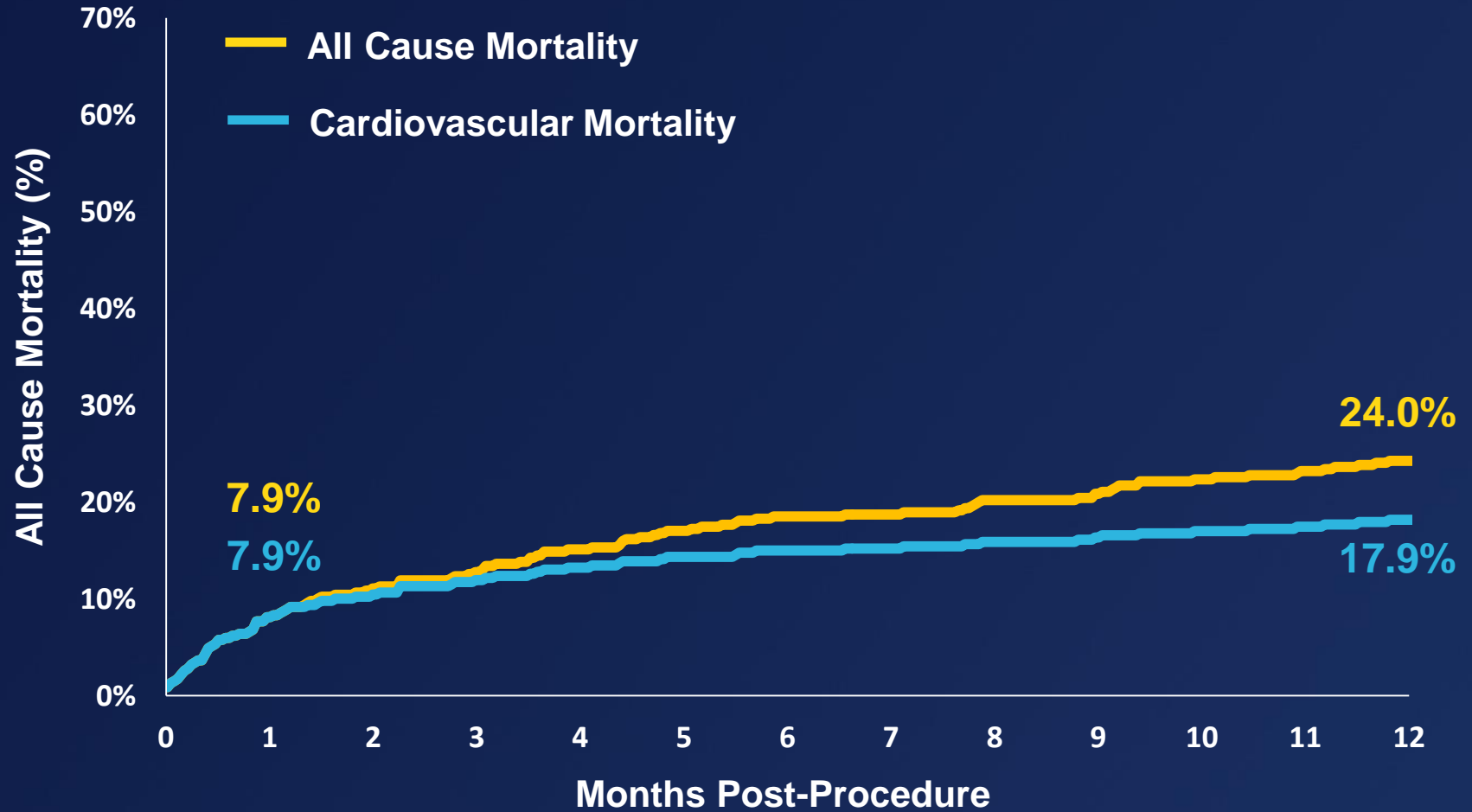
Disability Factors	N=471
Assisted Living, %	27.8
Katz Score (Index of ADLs), %	
≥ 1 ADLs Deficits, %	28.5
≥ 2 ADLs Deficits, %	21.0
≥ 3 ADLs Deficits, %	13.8
Mini-Mental Score (MMSE Score 0–30)	26.0 ± 3.2
Dementia (Based on MMSE)	
None (≥ 25), %	72.1
Mild (21–24), %	22.6
Moderate or Severe (< 20), %	5.3
Wheelchair Bound, %	16.8

# CoreValve Extreme Risk Iliofemoral Results

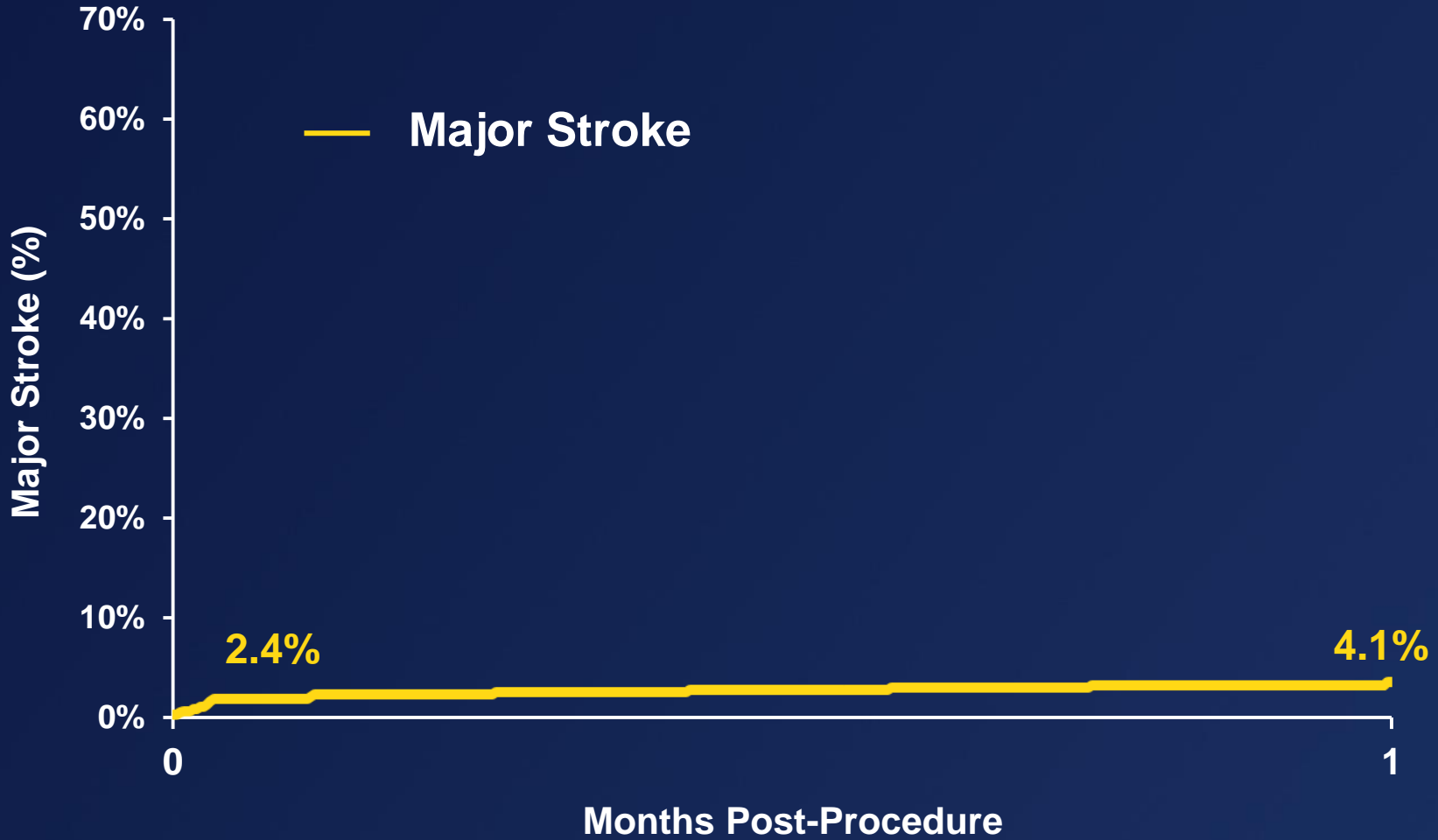
# Primary Endpoint



# 1 Year Mortality



# Major Stroke





# Secondary Endpoints

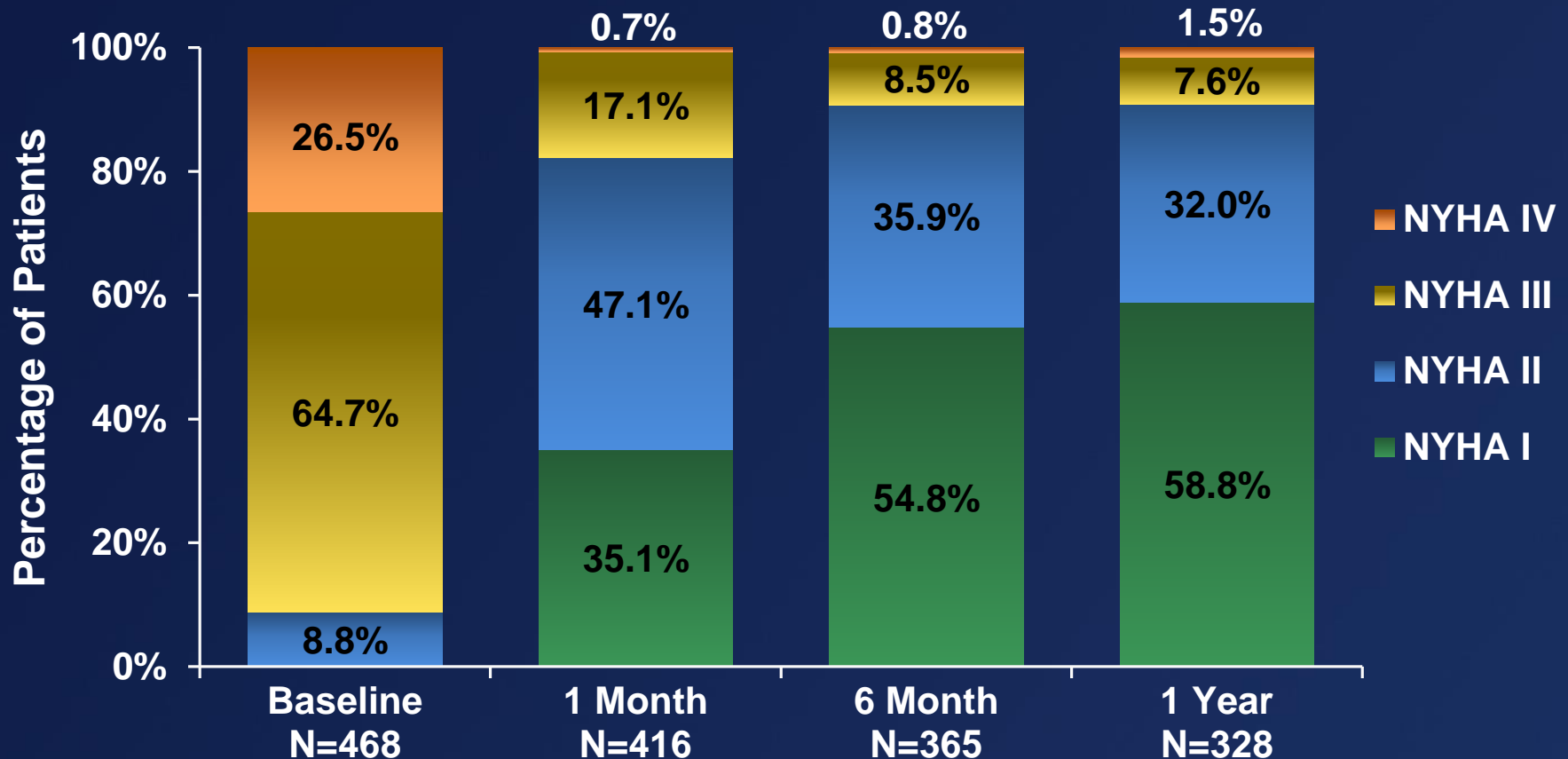
Events*	1 Month	1 Year
Any Stroke, %	3.9	6.7
Major, %	2.4	4.1
Minor, %	1.7	3.1
Myocardial Infarction, %	1.3	2.0
Reintervention, %	1.3	2.0
VARC Bleeding, %	35.1	41.4
Life Threatening or Disabling, %	11.7	16.6
Major, %	24.1	27.6
Major Vascular Complications, %	8.3	8.5
Permanent Pacemaker Implant, %	22.2	27.1
Per ACC Guidelines, %	17.4	19.9

\* Percentages obtained from Kaplan Meier estimates

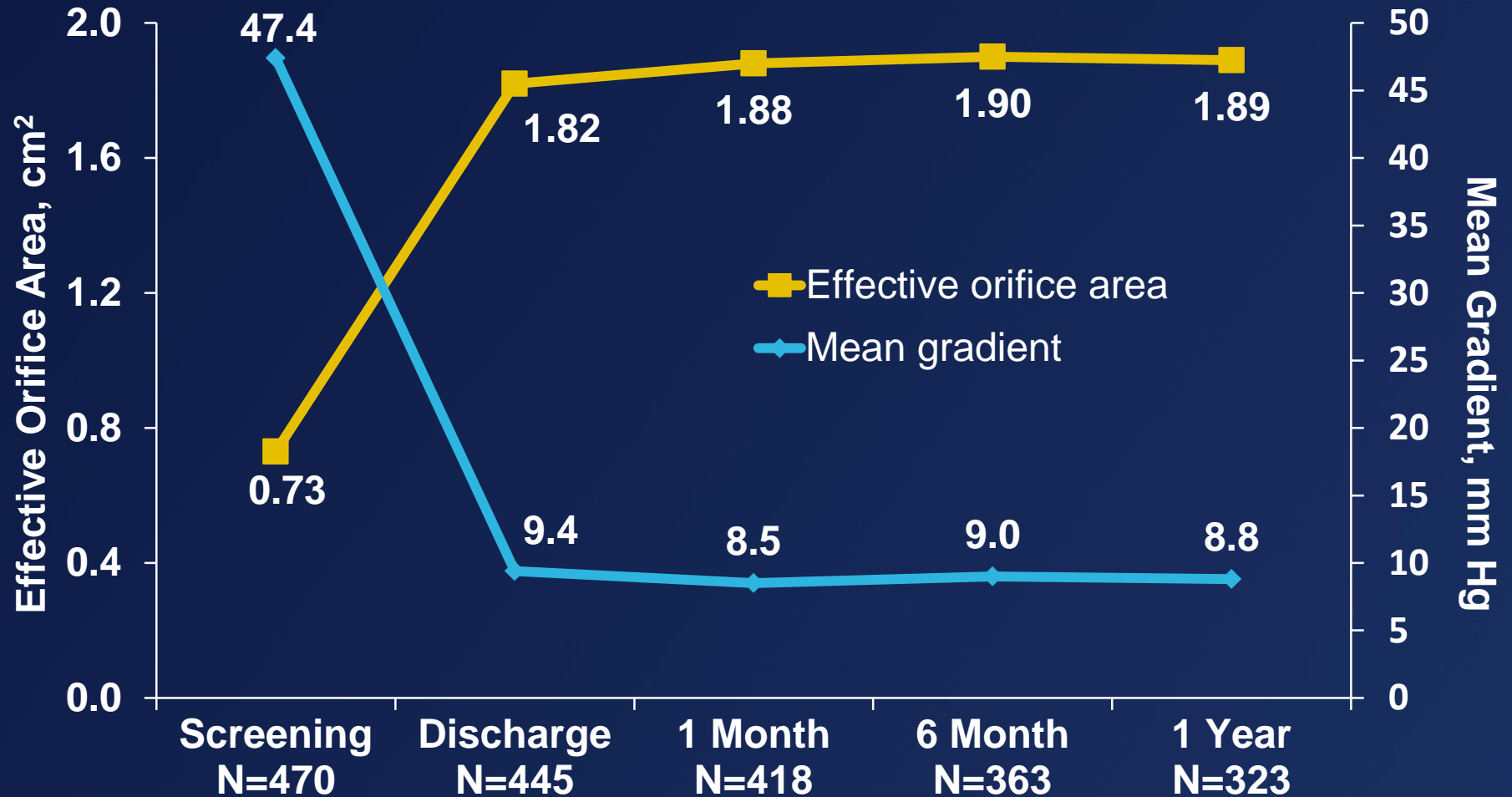
# NYHA Class Survivors

90% of Patients Improved at Least 1 NYHA Class by 1 Year

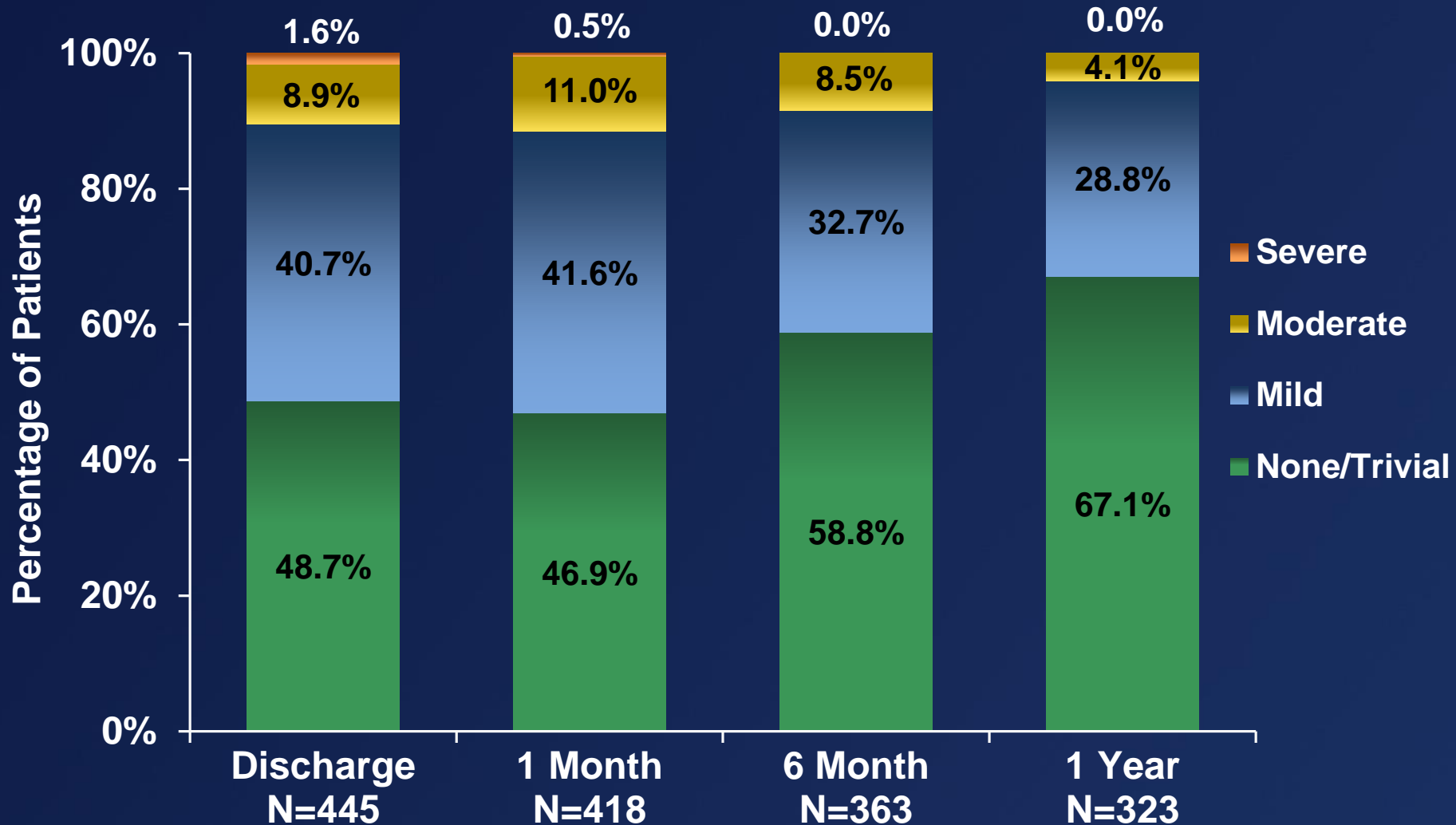
60% of Patients Improved at Least 2 NYHA Classes by 1 Year



# Echocardiographic Findings

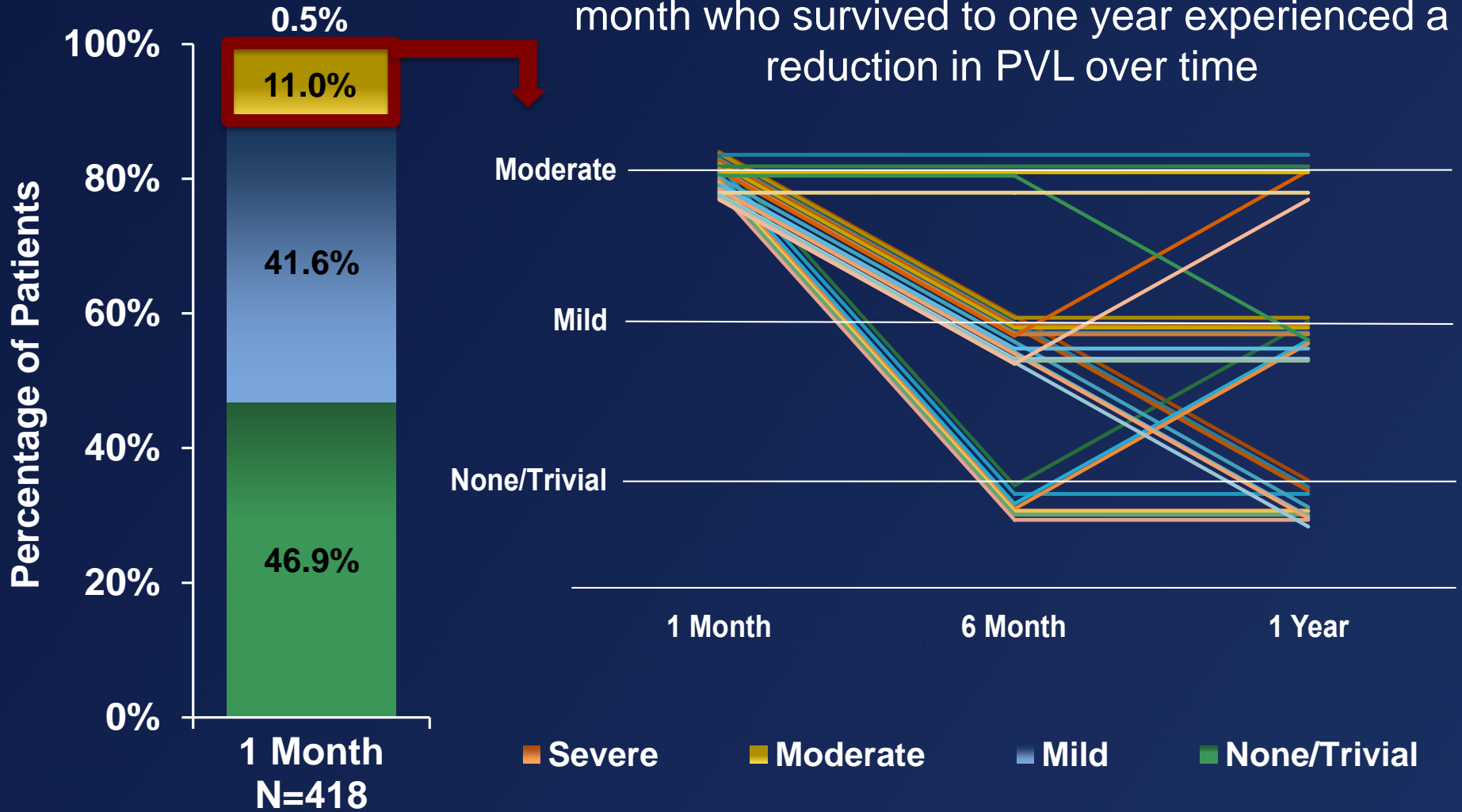


# Paravalvular Regurgitation



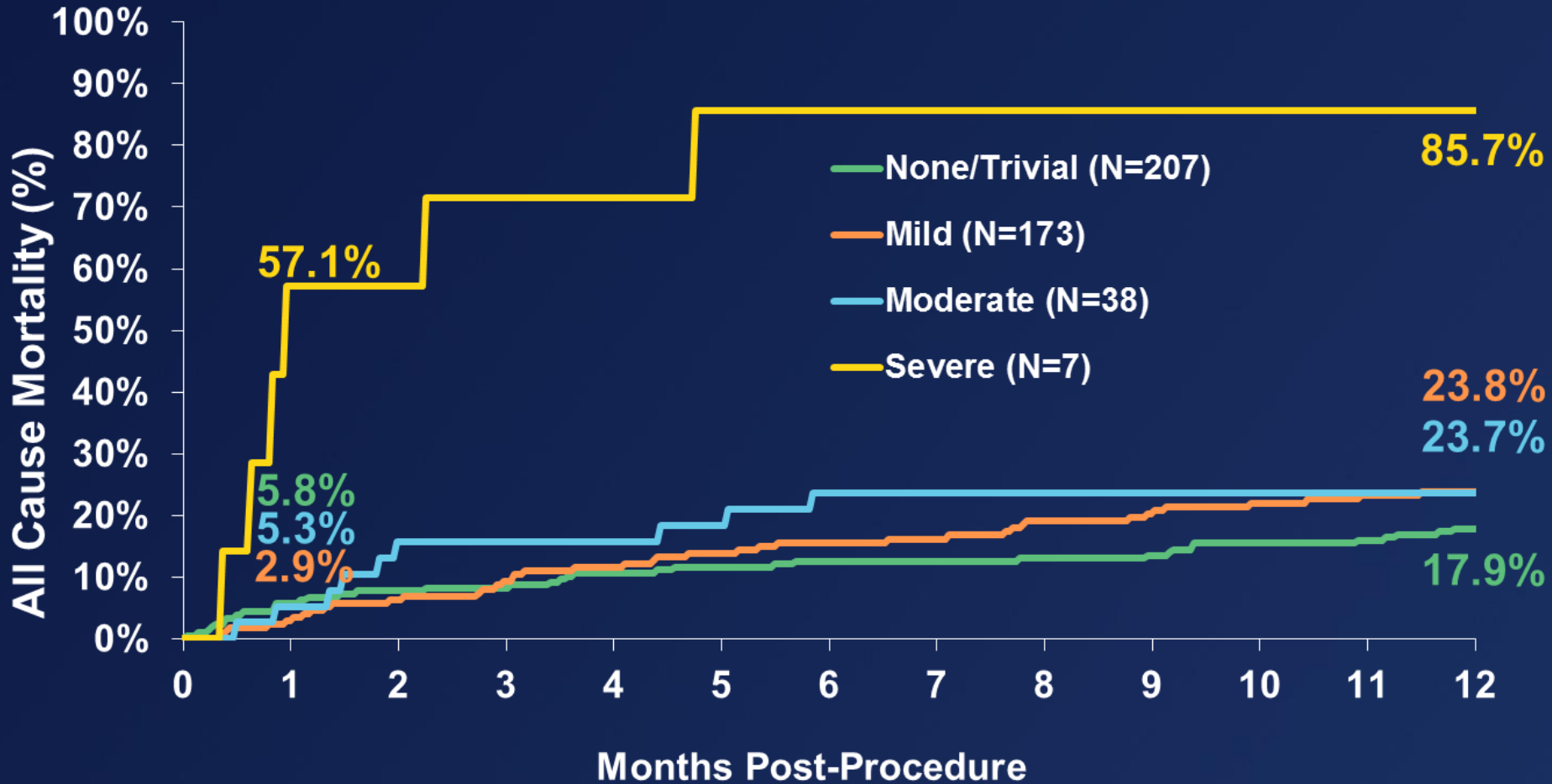
# Paravalvular Regurgitation

80% of patients with moderate PVL at one month who survived to one year experienced a reduction in PVL over time



# Impact of PVL on Late Mortality











Log rank P Value <0.0001



# Primary Endpoint Predictors-I

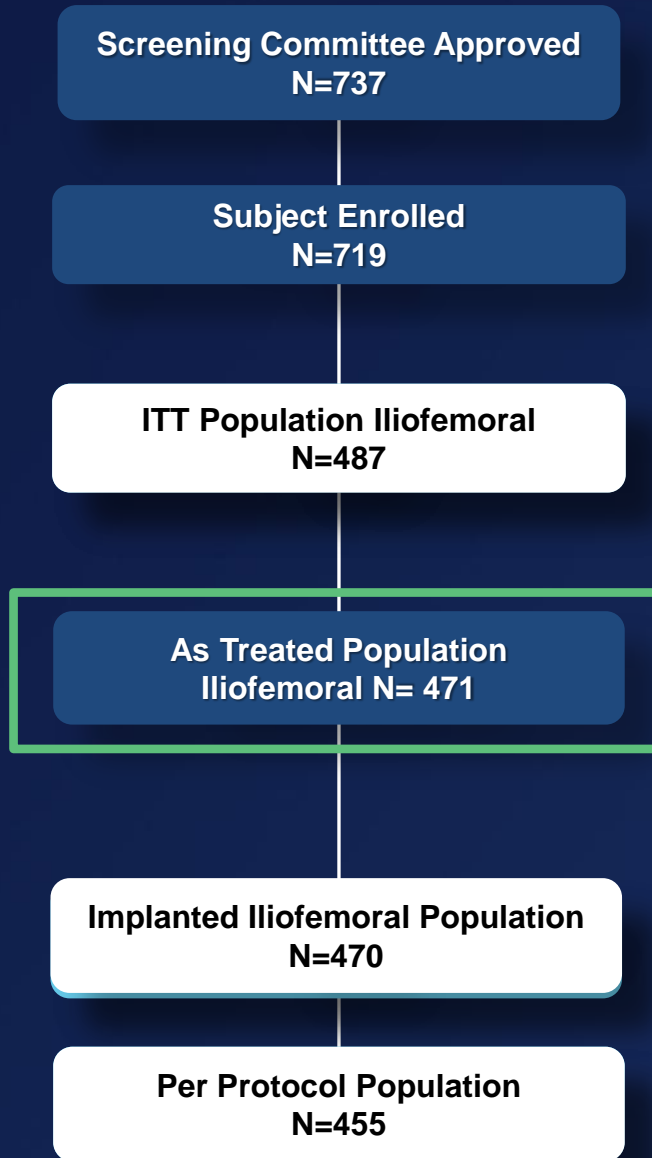
Variable	Patients	KM (%) 1-Yr (95% CI)	Rate of All Cause Mortality or Major Stroke (25.5%)	P Value
<b>Gender</b>				
Male	231	28.6 (22.8, 34.5)		0.1259
Female	240	22.5 (17.2, 27.8)		
<b>Age</b>				
>85	249	27.3 (21.8, 32.9)		0.2575
≤85	222	23.5 (17.9, 29.0)		
<b>Baseline NYHA</b>				
II	41	17.1 (5.6, 28.6)		
III (vs. II)	303	24.1 (19.3, 28.9)		0.3473
IV (vs. II)	124	31.5 (23.3, 39.7)		0.1022
<b>STS Score</b>				
<10	263	23.2 (18.1, 28.3)		
10-15	125	23.2 (15.8, 30.6)		0.9438
>15	83	36.1 (25.8, 46.5)		0.0242

# Primary Endpoint Predictors-II

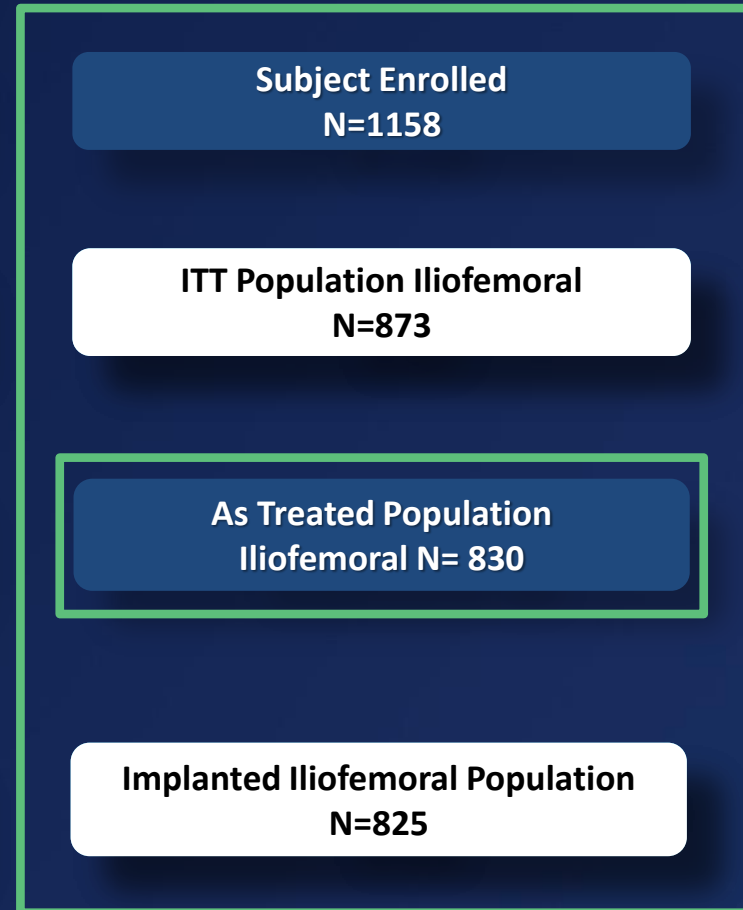
Variable	Patients	KM (%) 1-Yr (95% CI)	Rate of All Cause Mortality or Major Stroke (25.5%)	P value
Baseline LVEF				
<40	79	29.1 (19.1, 39.1)		0.3849
≥40	390	24.7 (20.4, 28.9)		
Hypertension	424	26.0 (21.8, 30.1)		0.5525
Diabetes	200	27.6 (21.4, 33.8)		0.4043
CAD	386	28.5 (24.0, 33.0)		0.0028
Prior Stroke	65	30.8 (19.6, 42.1)		0.2990
Prior MI	147	29.3 (21.9, 36.7)		0.1756
CLD/COPD	277	26.0 (20.9, 31.2)		0.7832
Assisted Living	131	36.7 (28.4, 45.0)		0.0003
PVD	165	30.4 (23.3, 37.4)		0.0847



# Continued Access Study

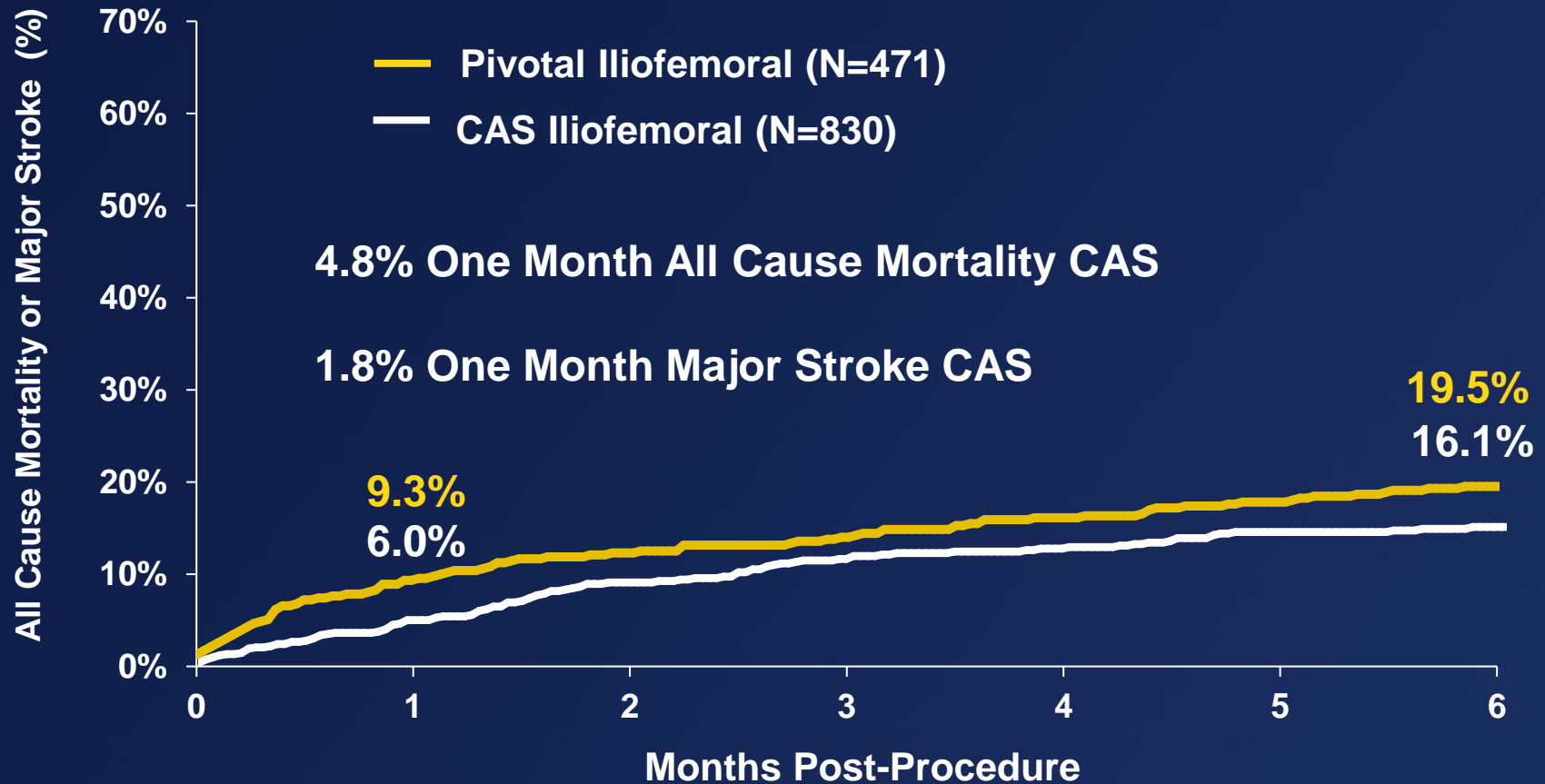


## Continued Access Study



# 6 Month Mortality or Major Stroke

## All Cause Mortality or Major Stroke



## Conclusions - I

- 471 patients deemed extreme risk for surgical aortic valve replacement by two cardiac surgeons confirmed by external surgical review
- Detailed analysis of co-morbidity, frailty, and disability confirmed unsuitability for surgical AVR
- The CoreValve Extreme Risk Study achieved its primary endpoint of a reduction in all cause mortality or major stroke at one year compared to a rigorously defined OPG

## Conclusions - II

- Low rates of major stroke at 1 month and one year
- Low rate of moderate/severe aortic regurgitation that improved over time
- No association of mild/moderate PVL on late mortality
- Improved outcomes in Continued Access Study

# Summary

- The results from the US CoreValve Extreme Risk Iliofemoral Study support the safety and efficacy of this therapy who are deemed unsuitable for surgical aortic valve replacement