

Center for Devices and Radiological Health
CDRH

CIRCULATORY SYSTEM DEVICES PANEL

Friday, November 30, 2007

Thoratec Corporation

HeartMate II Left Ventricular Assist System

PMA P060040

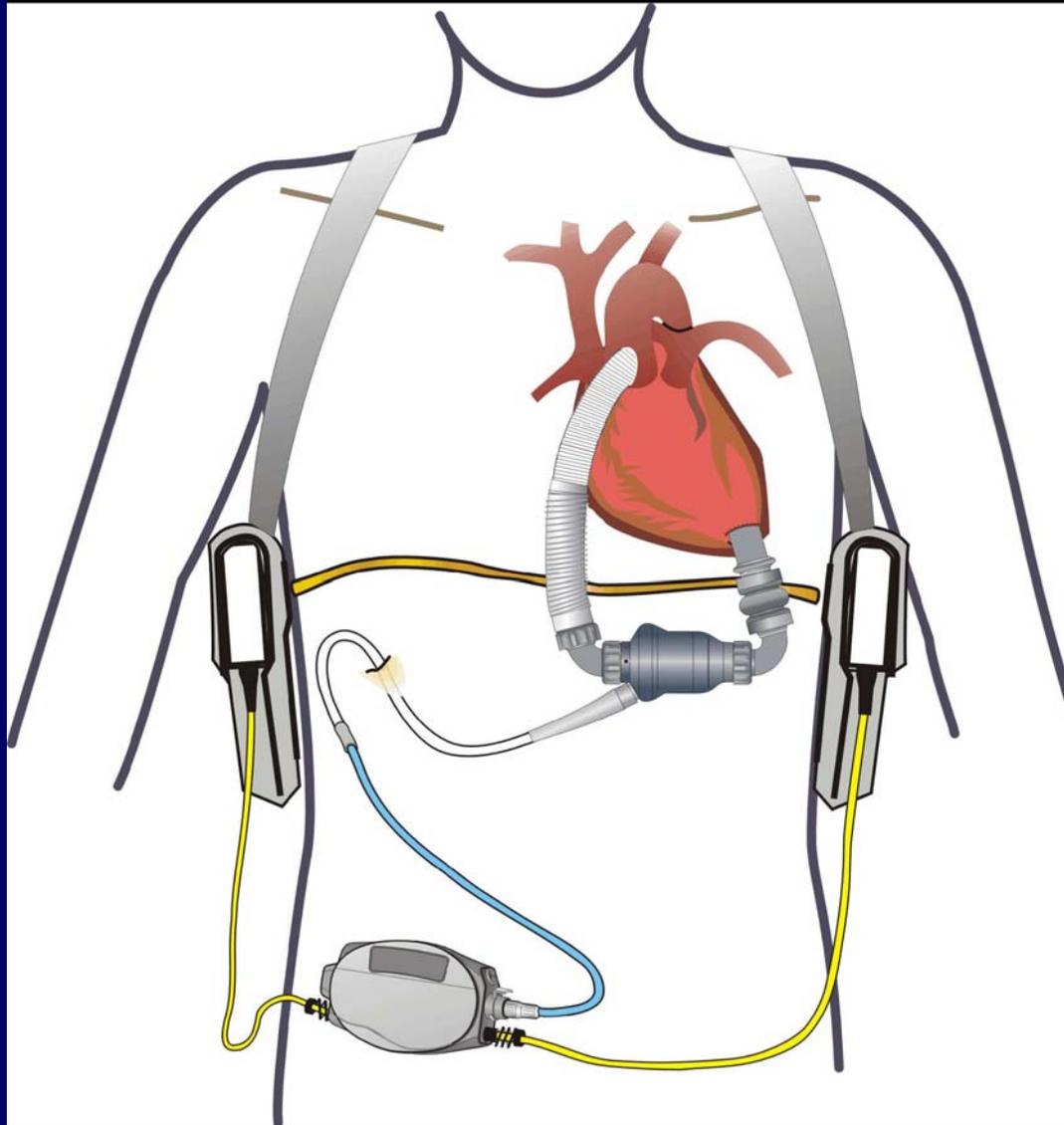
FDA Review Summary

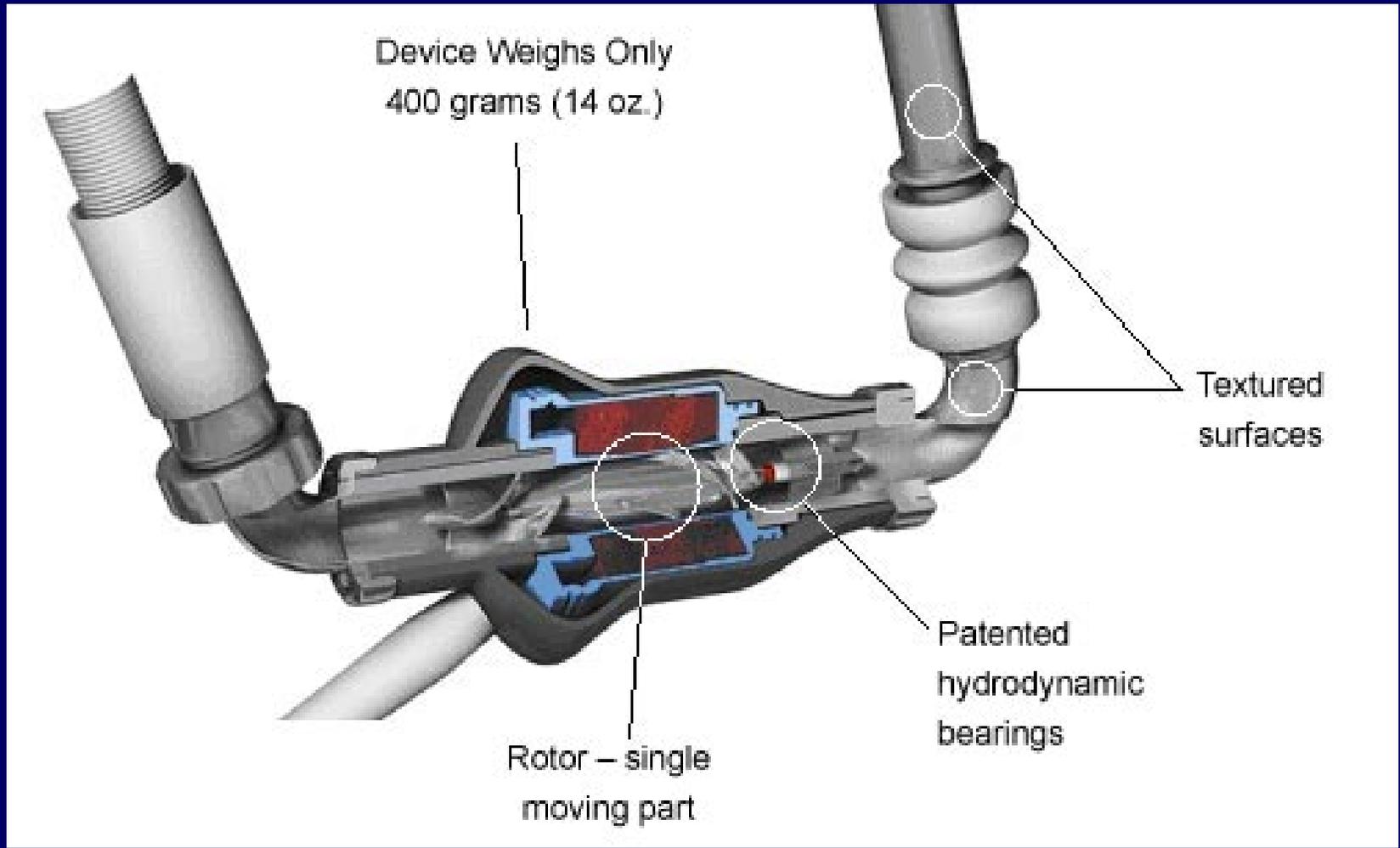
Thoratec Corporation
HeartMate II Left Ventricular Assist System

Eric Chen M.S.
FDA/CDRH/ODE/DCD

Overview of Presentation

- History of Clinical Study
- Pre-clinical Evaluation
- Clinical Evaluation
- Statistical Evaluation
- Post-Market Study Proposal
- Panel Questions





Mode of Operation

- Previous BTT devices were pulsatile, volume-displacement devices that fill and eject blood in a cyclic fashion that is analogous to the systole and diastole of the native heart
- Continuous-flow, rotary technology ejects a volume of blood by the speed of rotation of the impeller and the pressure differential that exists across the pump

Class III Device

- Provide reasonable assurance of safety and effectiveness (Federal Food, Drug, Cosmetic Act, §513(a)(1)(C))
- Relevant factors (21 CFR 860.7(b))
 - Patient population
 - Conditions of use
 - Probable benefit vs. probable injury
 - Reliability of the device

Proposed Indication for Use

The HeartMate II Left Ventricular Assist System (LVAS) is intended for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from non-reversible left ventricular failure. The HeartMate II LVAS is intended for use both inside and outside the hospital or for transportation of ventricular assist device (VAD) patients via ground ambulance, fixed wing aircraft, or helicopter.

The HeartMate II LVAS is contraindicated for patients whose body surface area is less than 1.3 m².

Preclinical Evaluation

(Determined To Be Satisfactory)

- Alarms
- Biocompatibility
- Electrical Safety and EMC
- Manufacturing
- Software
- Sterilization, packaging, shelf life, shipping

U.S. Clinical Study

- IDE G010230
 - Single-arm prospective, multi-center pivotal study
 - 133 implanted patients at 26 sites
 - The study was to be prospectively determined successful if the one-sided 95% lower confidence limit of the true success rate exceeded 65%, the Performance Goal

Three Patient Enrollment Groups

1. Primary Study Cohort

- 126 patients enrolled ($BSA \geq 1.5 \text{ m}^2$)

2. Continued Access Protocol Cohort (CAP)

- 138 patients enrolled ($BSA \geq 1.5 \text{ m}^2$)
 - 58 patients have reached a clinical endpoint as of March 16, 2007

3. Small BSA Cohort

- 15 patients enrolled ($1.2 \text{ m}^2 \leq BSA < 1.5 \text{ m}^2$)
 - 7 patients enrolled in Primary Study Cohort
 - 8 patients enrolled in CAP
 - 10 patients have reached a clinical endpoint as of March 16, 2007

Device Replacements

- 7 device replacements (5 Primary, 2 CAP)
 - 4 patients received another HeartMate II
 - 3 patients received approved LVADs
- 4 replacements were caused by pump thrombosis - patients received another HMII
 - On post-implant days 0, 24, 56, and 123
- Other replacements: pledgets in the pump, outflow graft kink, poor inflow positioning - patients received other LVAD

Device Malfunctions/Failures

A total of 108 suspected device malfunctions were reported with the initial submission

- 19 events were determined to not be malfunctions/failures
- Of the 68 reported malfunctions
 - 13 related to implanted components
 - 55 related to external components
- 21 events related to technical errors during implantation, user error, or wear and tear

Engineering Conclusions

- Pre-clinical testing demonstrate performs according to specifications.
- Corrective actions proposed for the malfunctions/failures.
- Technical errors may reduce with more experience.
- The reduced pulsatile effects of the pump have not produced any observed physiological problems but our experience is still limited.

FDA Review Team

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Clinical Review

HeartMate II LVAS

Julie Swain M.D.

Cardiac Surgery

Ileana Piña M.D.

Heart Failure Cardiology

FDA-APPROVED BTT LVADs (5 Devices)

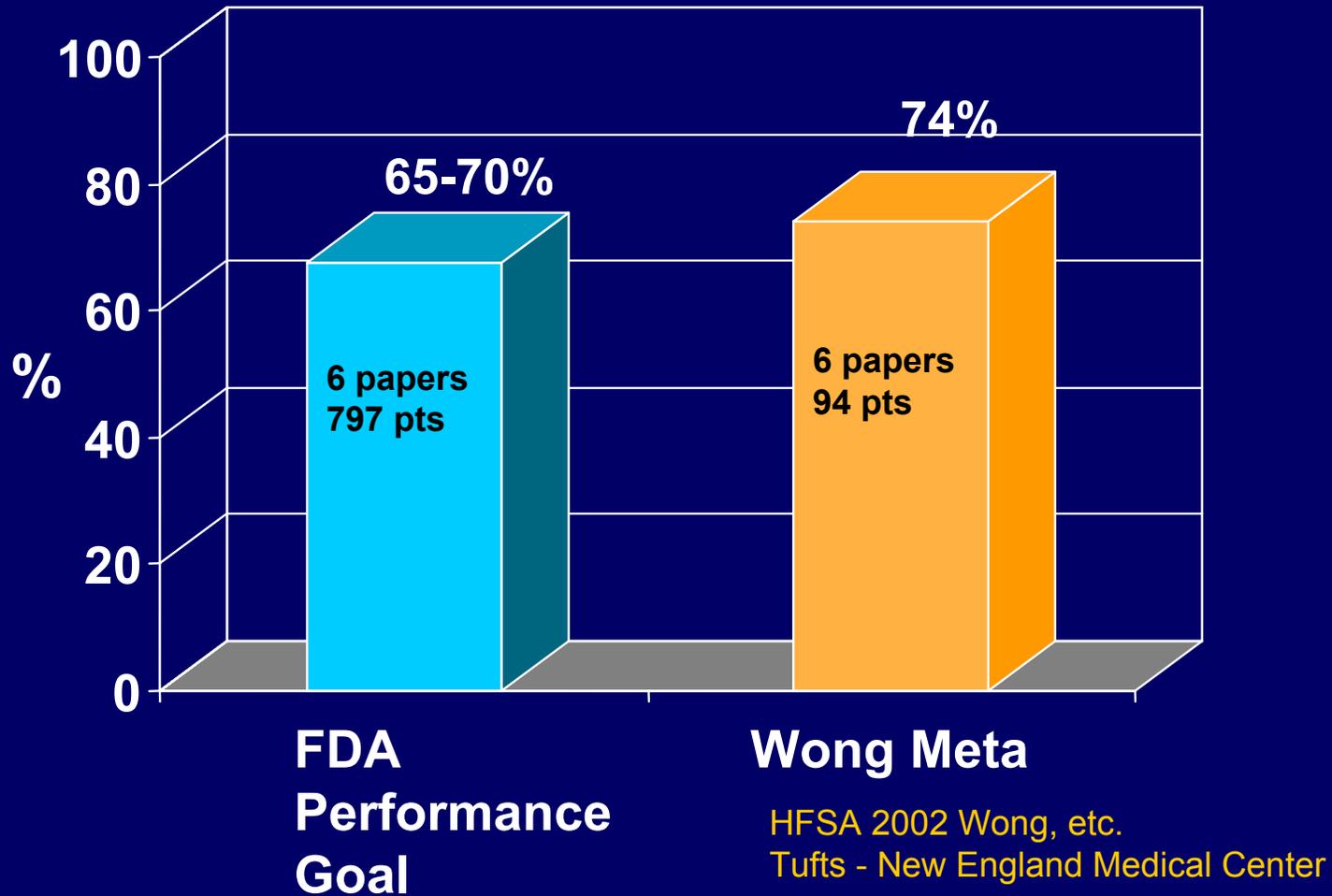
- None were randomized, controlled studies
- None had comparable control groups
- In 2002, FDA developed a Performance Goal of survival to transplant

LVAD BTT Performance Goals (Literature Search)

Criteria for Inclusion:

- Bridge to transplant indication, LVAD (no RVAD or BiVAD)
- One of the 4 approved devices was used
- Published in 1997 or after [thus representing patients mostly studied after 1993-5]
- Series must have at least 20 patients, adults only
- Peer reviewed journals, no abstracts, must have original data
- English, Includes OUS data, wide geographic distribution
- Detailed enough data to determine results in adult patients with LVAD

LVAD BTT Performance Goal: “Survival to Transplant”



HMII Study Design

- **Multi-center single-arm clinical trial compared to a Performance Goal (PG)**
- **Primary Endpoint - prespecified, agreed-upon:**
 - Survival to cardiac transplantation **OR** 180 days of LVAD support while remaining transplant listed as a status 1A or 1B
- **Statistical Hypothesis:**

Ho: $P \leq 65\%$ vs. Ha: $P > 65\%$

where P is the lower confidence limit (LCL) of the proportion of successful patients in the intended patient population

UNOS Listing Criteria

Policy 9

- Status 1A
 - Mechanical Circulatory Support (MCS) for acute hemodynamic decompensation
 - MCS with objective medical evidence of significant device-related complications
 - Continuous mechanical ventilation
 - Continuous infusion of intravenous inotropes and continuous hemodynamic monitoring of left ventricular filling pressure
- Status 1B
 - Implanted MCS
 - Continuous infusion of intravenous inotropes
- Status 7
 - Temporarily unsuitable to receive a thoracic organ transplant

PMA Study Groups

1. Primary Study Cohort

- 126 patients enrolled ($BSA \geq 1.5 \text{ m}^2$)

2. Continued Access Protocol Cohort (CAP)

- 58/138 patients enrolled had reached a clinical endpoint as of March 16, 2007

3. Small BSA Cohort (Primary + CAP)

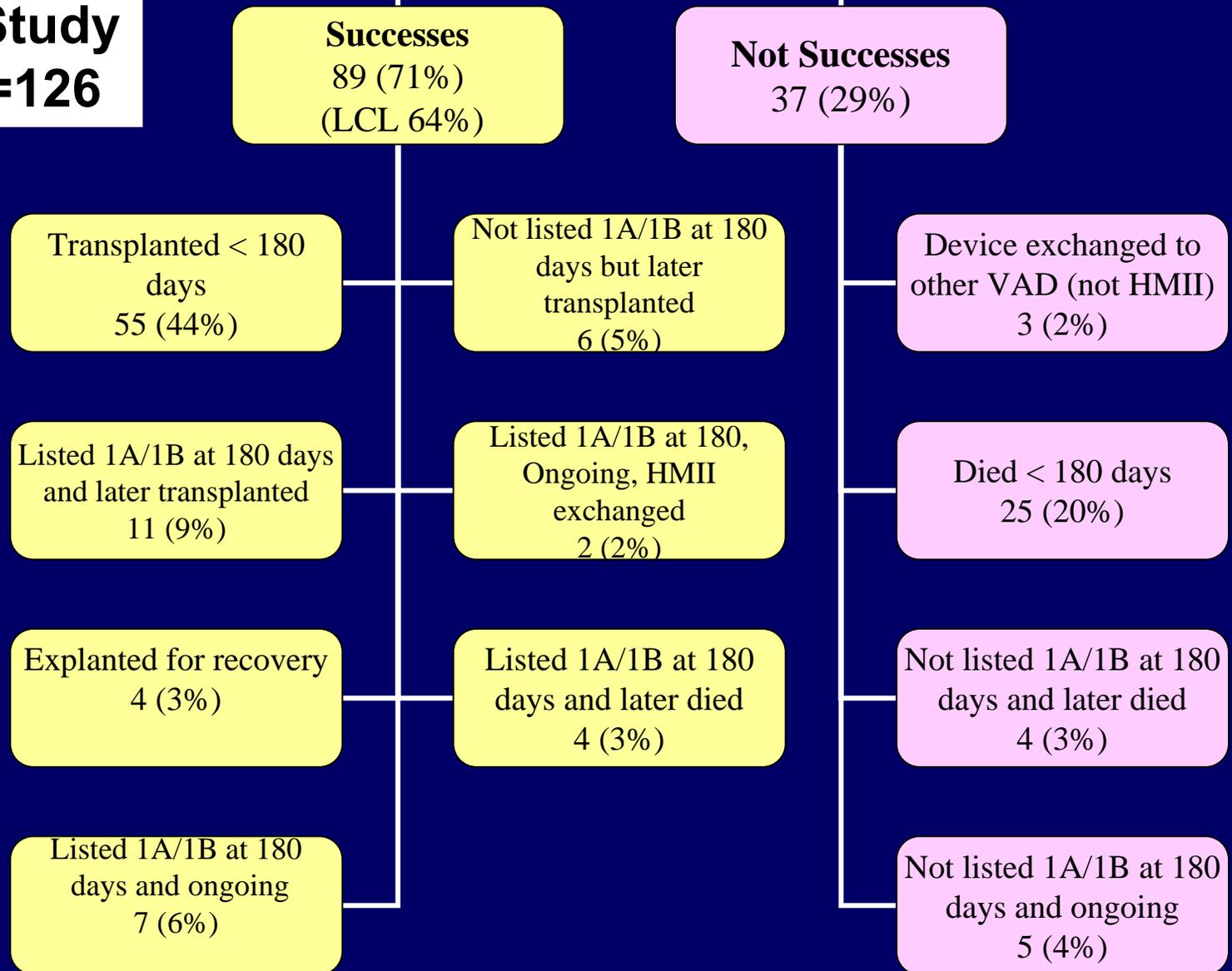
- 10/15 patients enrolled ($1.2 \text{ m}^2 \leq BSA < 1.5 \text{ m}^2$) had reached a clinical endpoint as of March 16, 2007

Baseline Characteristics

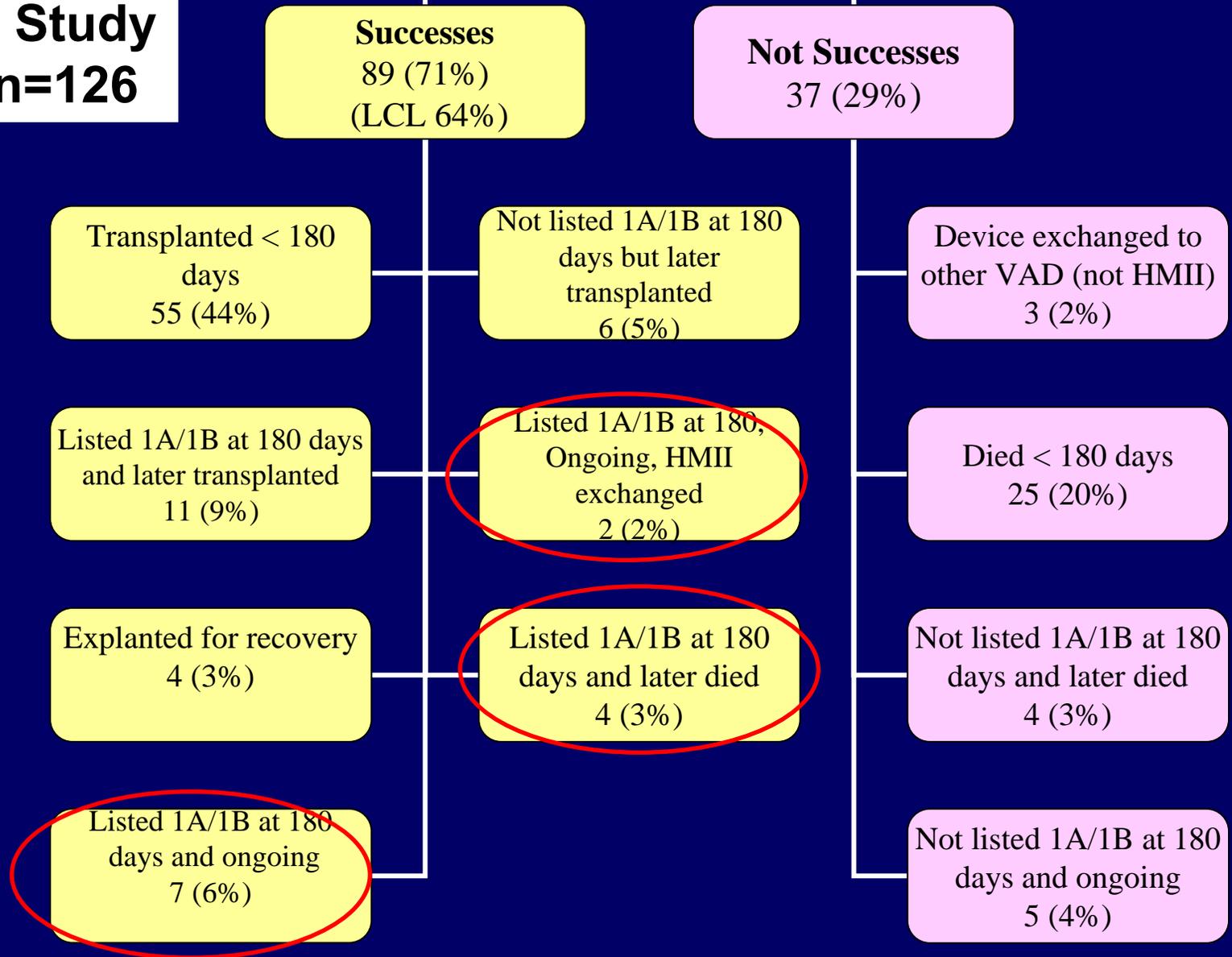
(n=126)

Mean age (years)	50.4
Male/Female (%)	83/17
Caucasian (%)	71
Black / Hispanic / Other (%)	21 / 6 / 2
Etiology	
Ischemic / Non-Ischemic / Other (%)	39 / 52 / 9
NYHA Class IV (%)	99
Total Bilirubin (mg/dL)	1.3
Creatinine (mg/dL)	1.4
Sodium (mM/L)	133.0

Primary Study Cohort n=126



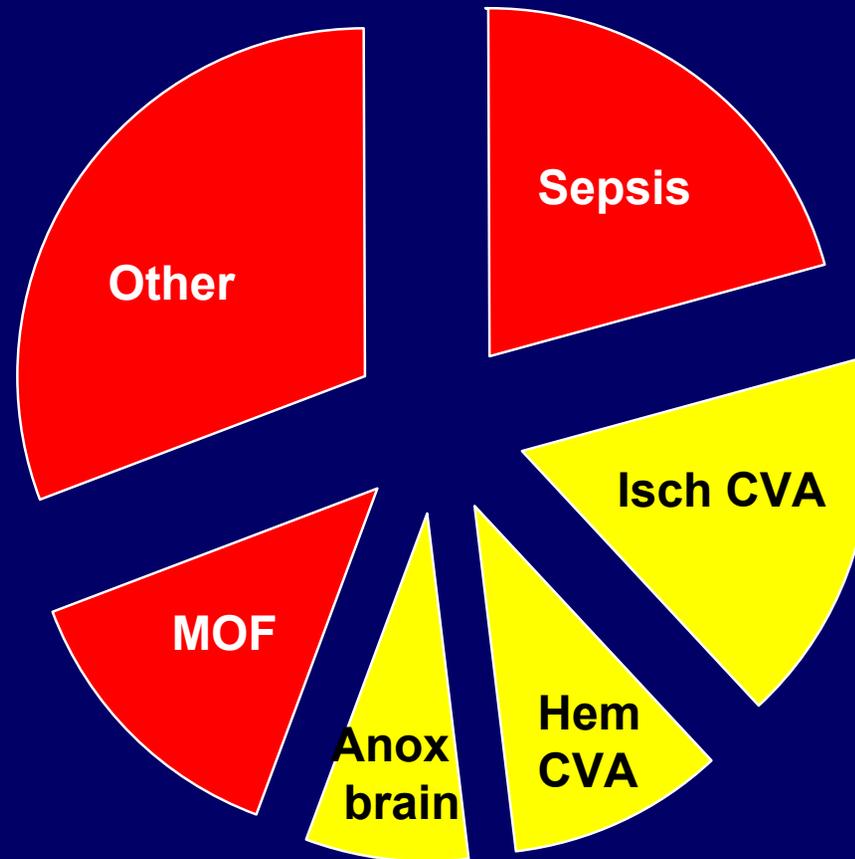
Primary Study Cohort n=126



Causes of Death

(29 Deaths)

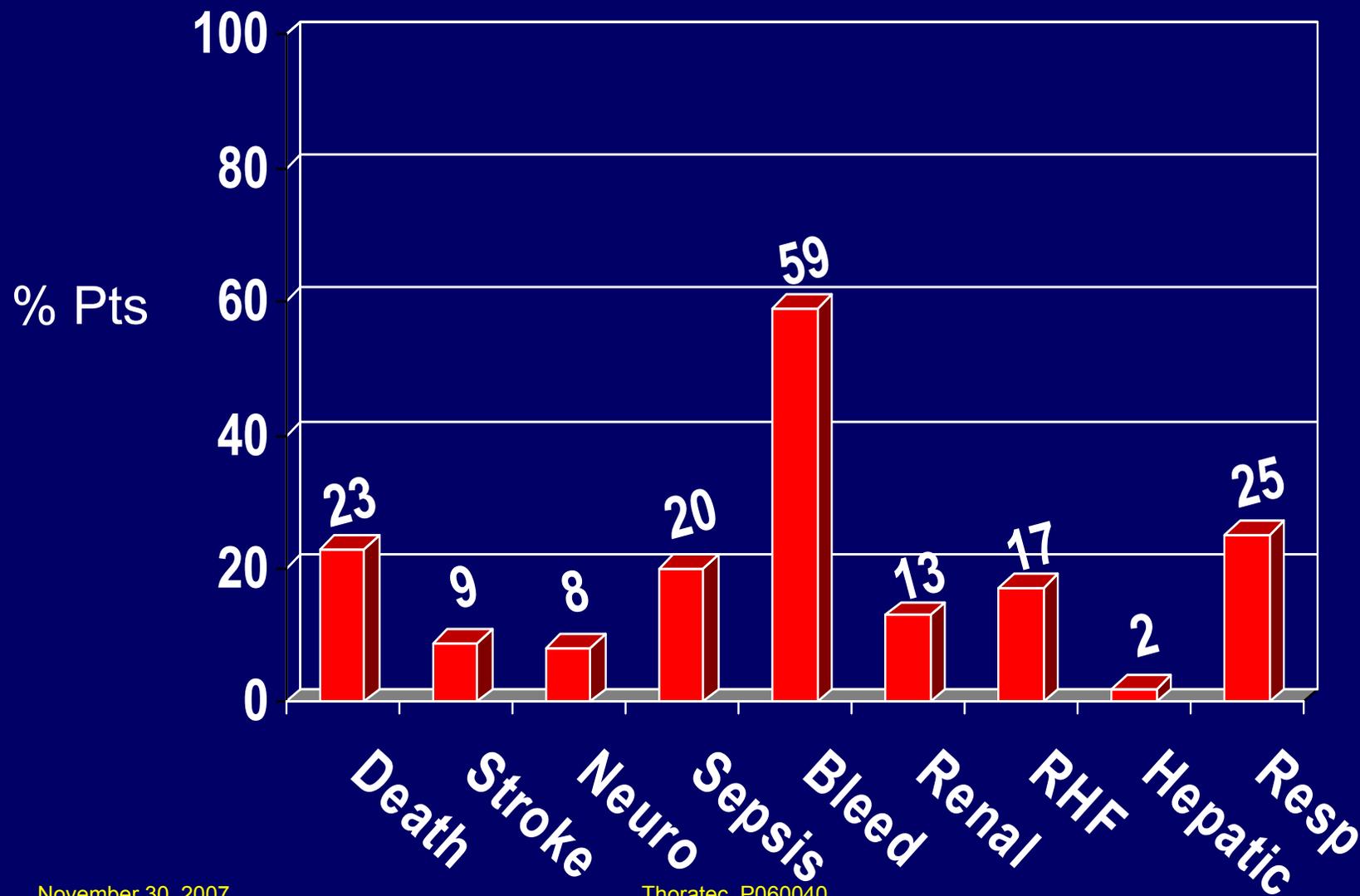
- Other**
- External device
- Implant device
- Right HF
- Bleed
- Respiratory
- CA
- Unknown



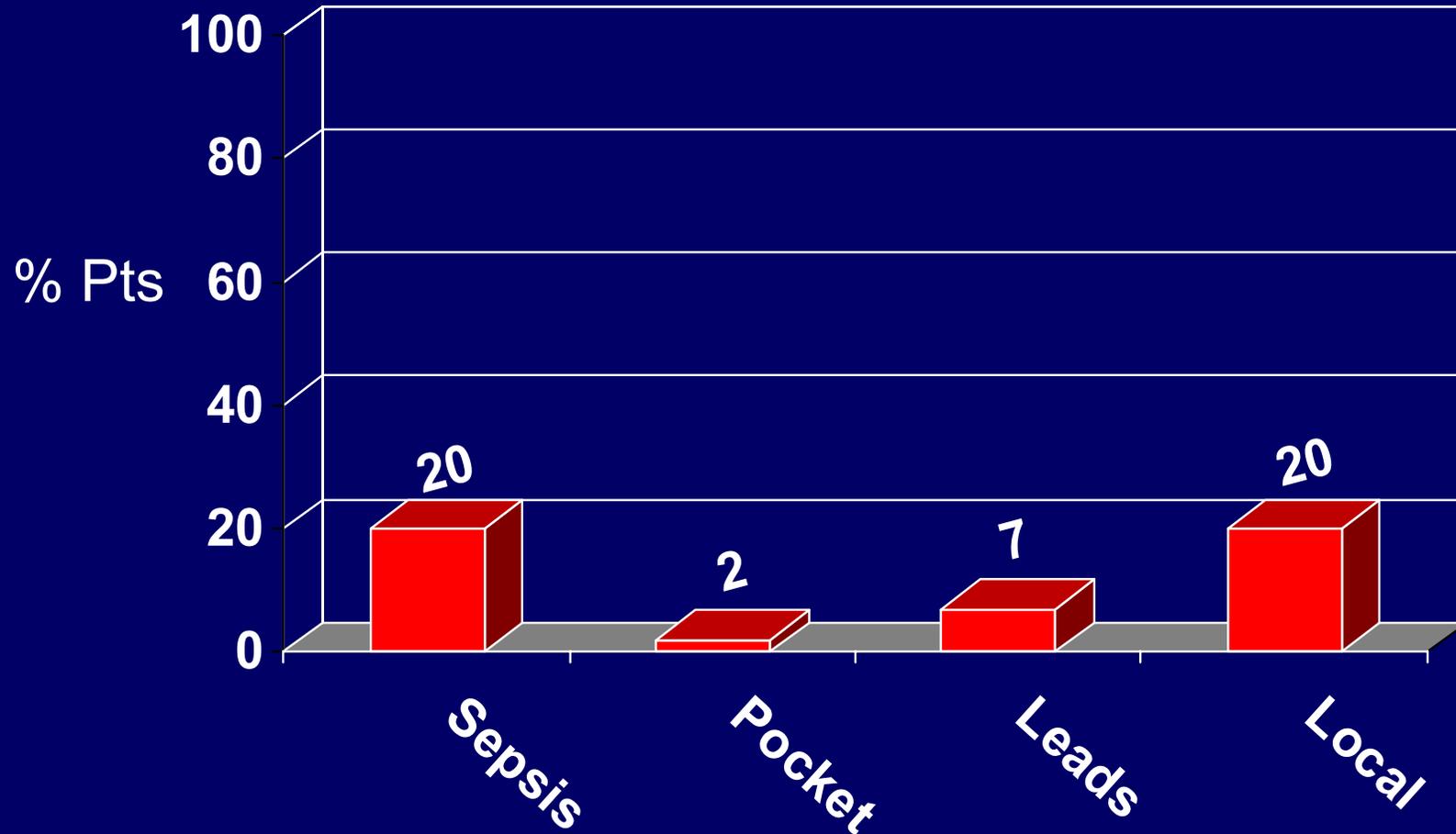
Adverse Events

- Difficult to develop a performance goal for AE's
 - No definitions listed in some studies
 - Different definitions in other studies
 - Rates differ among approved devices
 - Rates for same device change over time

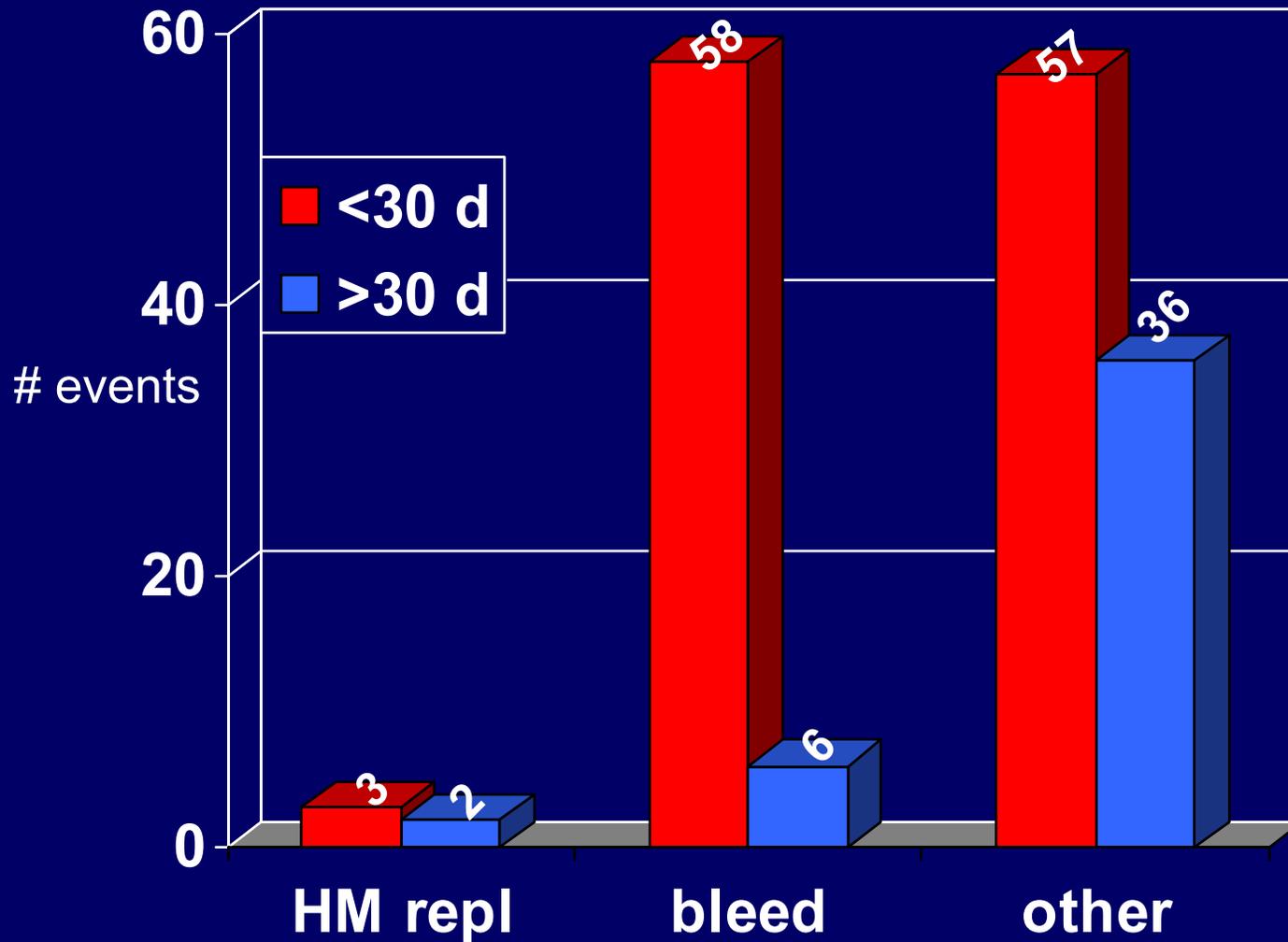
Serious Adverse Events



Infection



Reoperations



Pts. At risk (% w event)
<30d = 126 (57%)
>30d = 107 (23%)
Total 63%

Serious Adverse Events

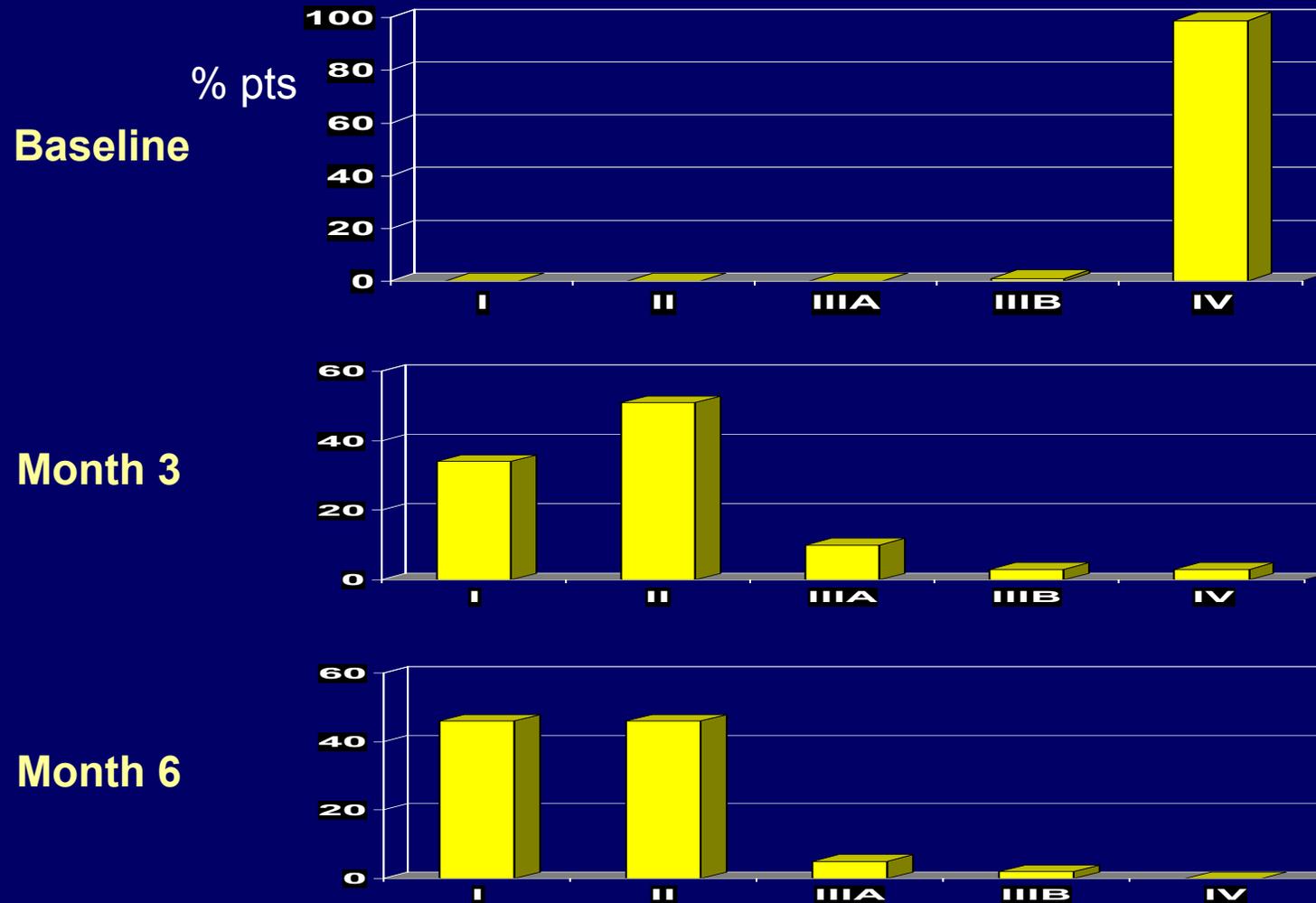
Adverse Event	# Events	% Pts
Device		
Device Thrombosis	2	2%
Hemolysis	3	2%
Confirmed Malfunctions	8	6%
Myocardial Infarction	1	1%
Cardiac Arrhythmias	55	44%
Peripheral TE	9	7%

Secondary Endpoints

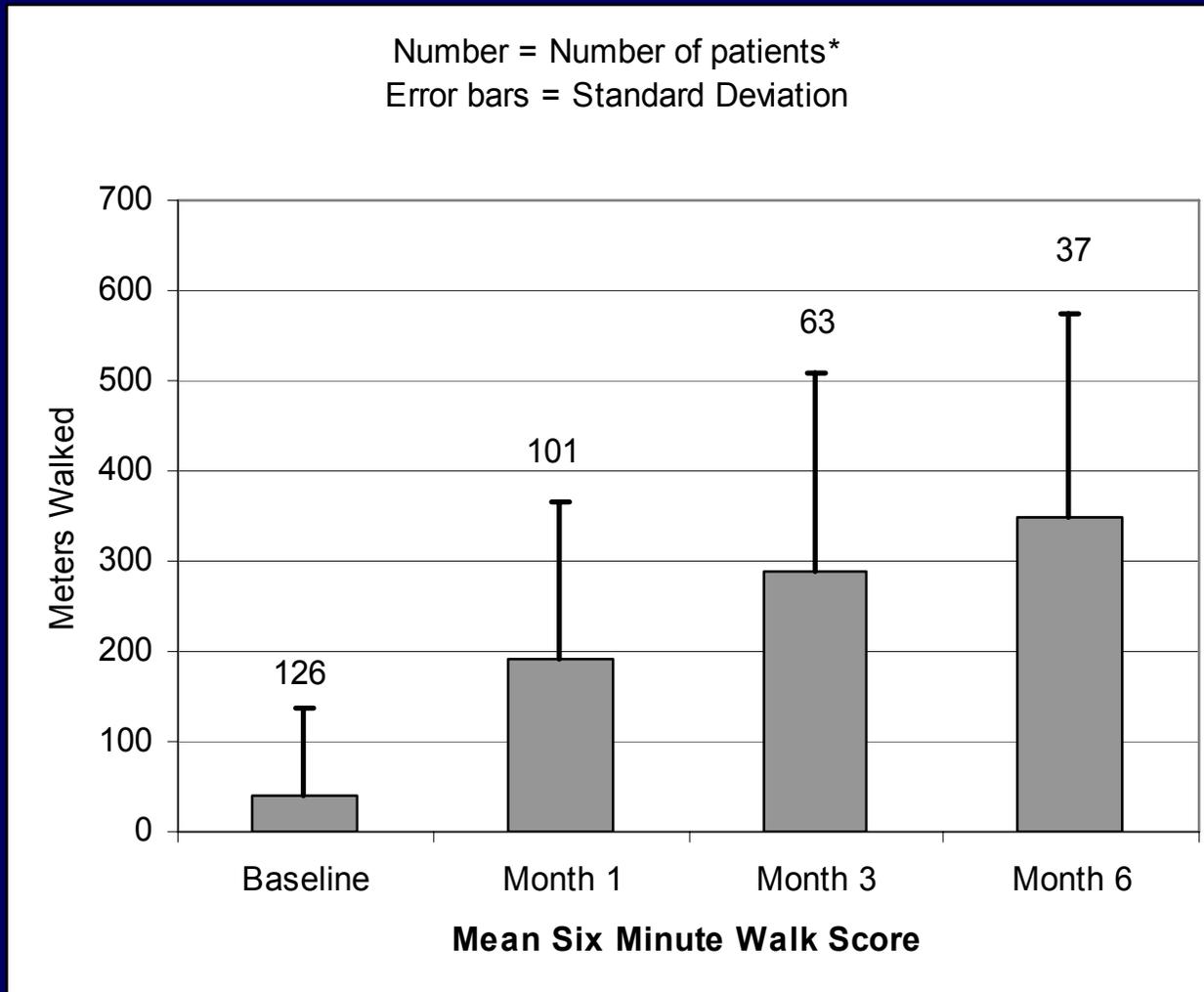
(no hypotheses, not for labeling)

- Survival to transplant
- Survival to 30-days and 1 year post transplant
- Quality of life/neurocognitive evaluation
- Functional evaluation
- Frequency of adverse events and reoperations
- Device reliability
- Adverse events

NYHA Class

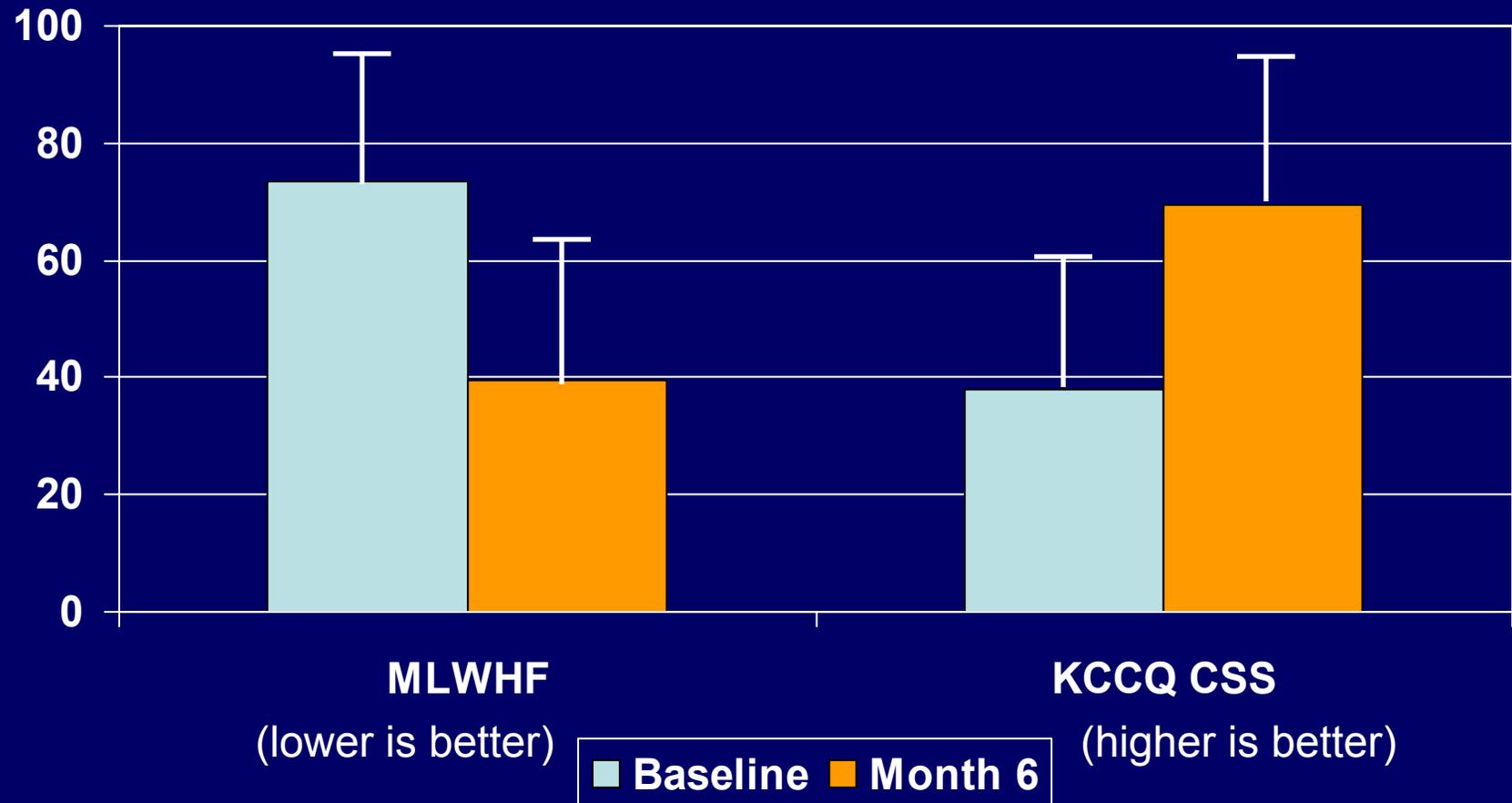


6 Minute Walk



* Patients with data who performed test, or who are medically unable to perform test and assigned zero

Quality of Life

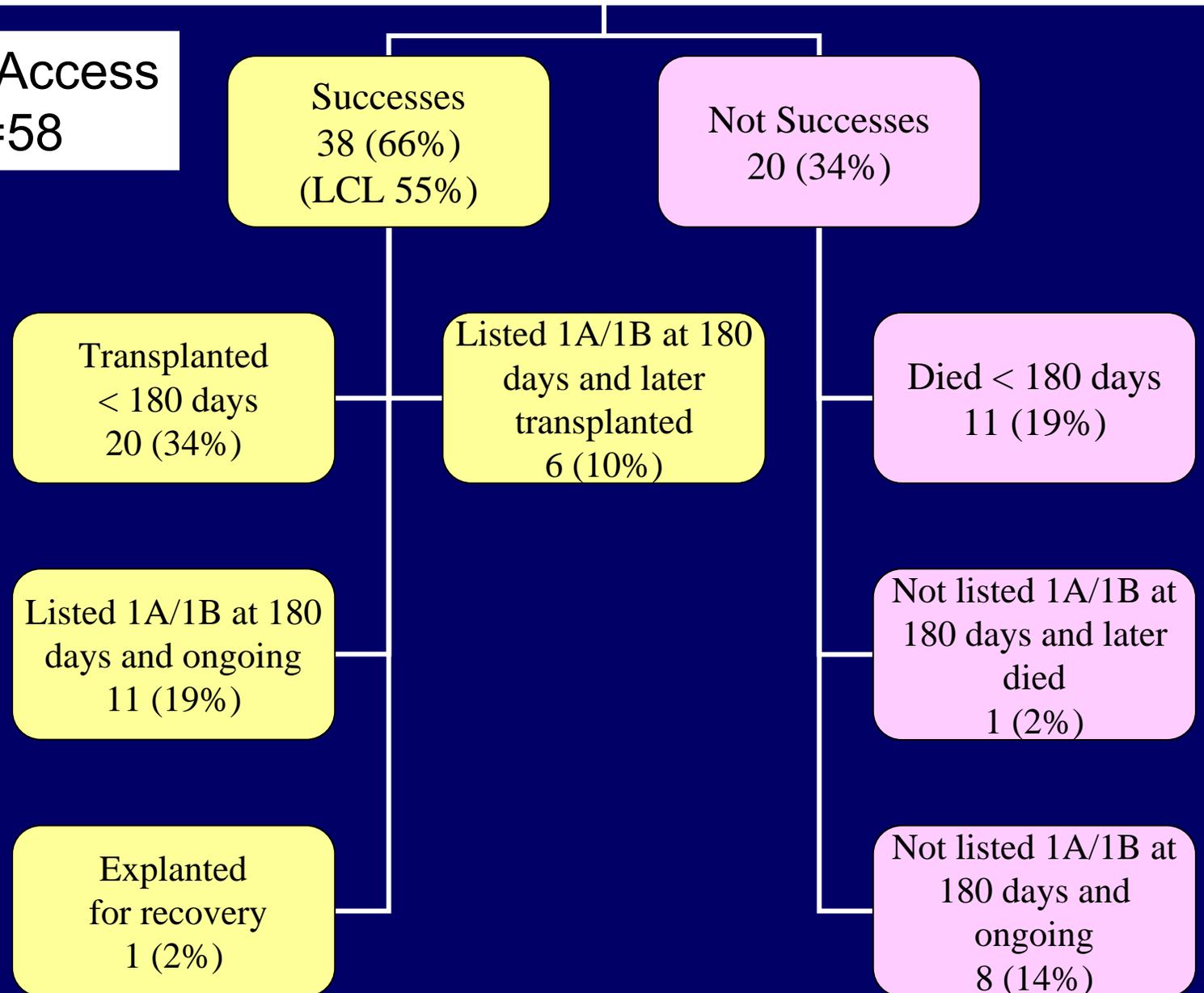


n=126 patients at Baseline
n=41 patients at Month 6

Neurocognitive Evaluation

- Neurocognitive data collected at 11 sites (50% of enrolled patients)
- 5 cognitive domains evaluated
- In patients who were tested, no profound defects were found (25% missing data at 6 months)
- Only between 6 and 10 patients in each domain had paired baseline and 6 month data
- No conclusions regarding neurocognitive performance can be made

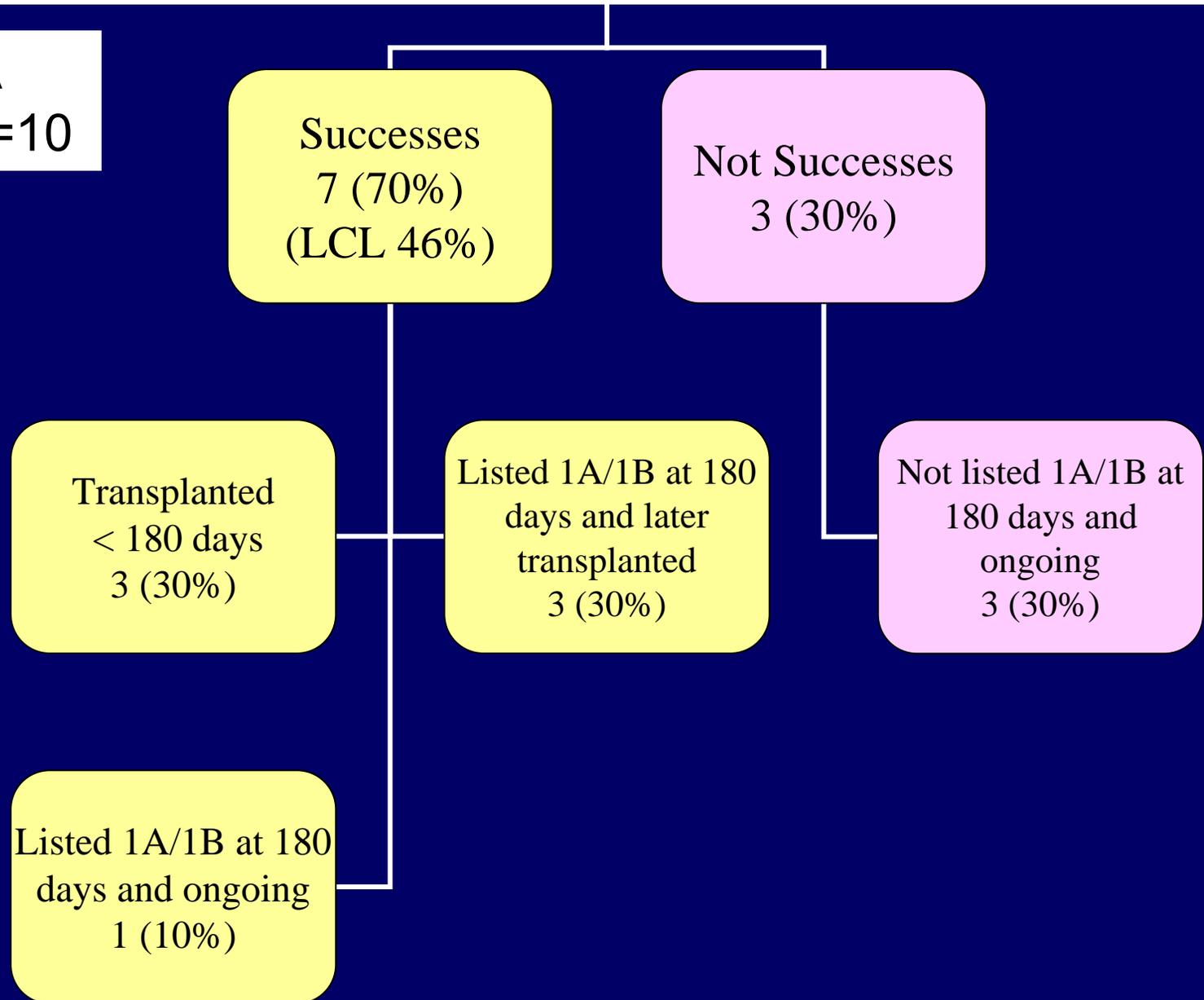
Continued Access Protocol n=58



Small BSA Cohort

- Small BSA Cohort: $1.2 \text{ m}^2 \leq \text{BSA} < 1.5 \text{ m}^2$ (n=7 from Primary + n=8 from CAP, 10 with results)
- No pre-specified analysis plan
- Data to be summarized and presented to FDA in the marketing application
- FDA to determine if labeling could be extended to this cohort.

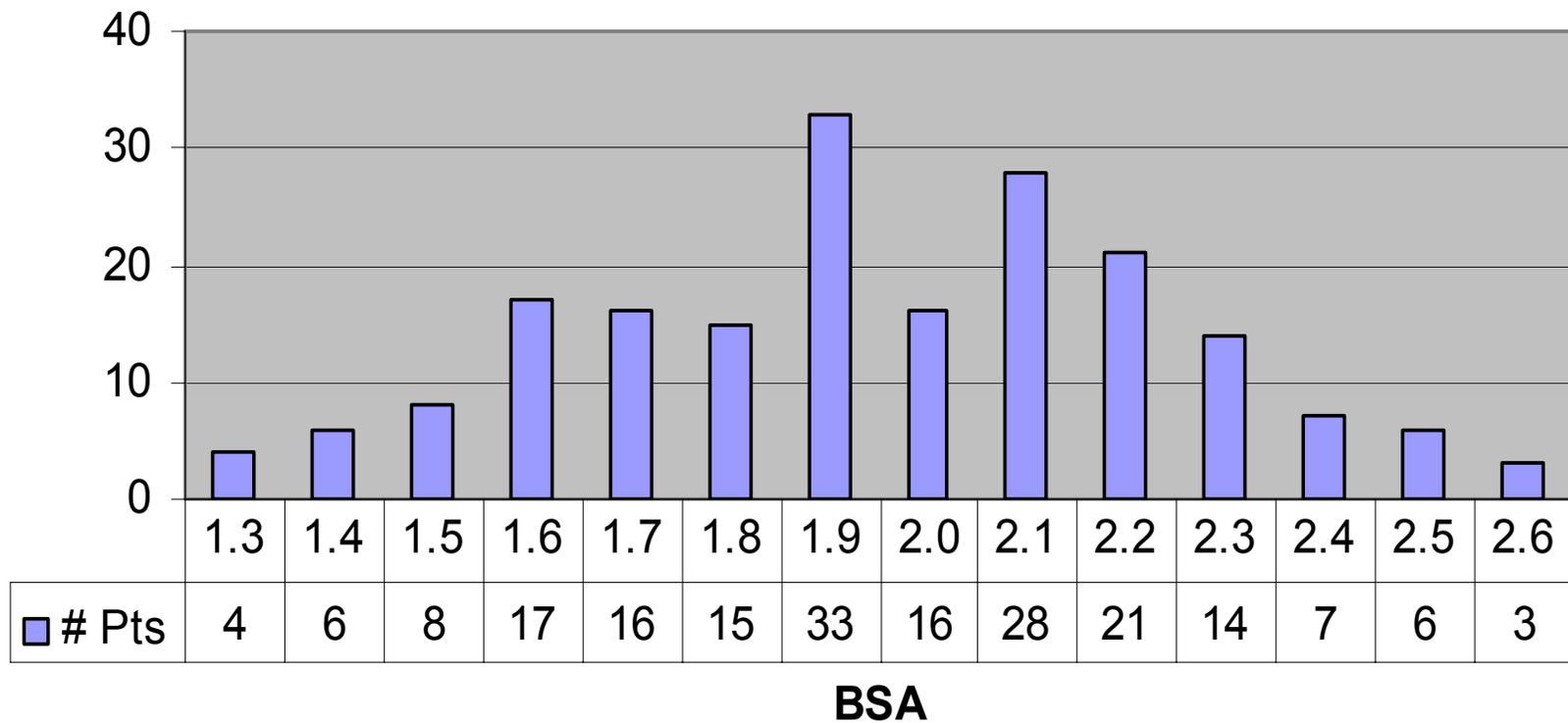
Small BSA
Patients n=10



Distribution of Body Surface Area

n=194 (126 Primary + 58 CAP + 10 small BSA) patients

Distribution of BSA



Secondary Endpoints/Adverse Events

The results for the CAP and Small BSA Cohorts are similar to that seen with the Primary Study Cohort.

Clinical Conclusions

- The HMII registry came close to meeting agreed upon primary endpoint of 65%****
- Safety results for this study were qualitatively within range expected from the literature
- The study was not powered to determine the effects of low pulsatility on end-organ or brain function
- The small sample size limits safety and effectiveness conclusions about small BSA patients

Gender and Mechanical Support

Study	Male	Female	Total	% female
Farrar et al	164	49	213	23%
Minami et al	164	19	183	10%
El Banayosy et al	250	33	283	12%
Frazier, et al	238	42	280	15%
Dibella et al	32	4	36	11%
HeartMate II (Primary Study)	105	21	126	17%
Total	953	168	1121	15%

Gender Analysis

n=194 (126 Primary + 58 CAP + 10 small BSA) patients
All 10 patients in the small BSA were women

	Male (n=150, 77%)	Female (n=44, 23%)
Caucasian	111 (74%)	26 (59%)
Ischemic	65 (43%)	14 (32%)
Total Bilirubin (mg/dL)	1.3	1.0
Creatinine (mg/dL)	1.5	1.2
Sodium (mM/L)	133.0	134.9
Incidence of Stroke	5%	18%
Reoperation after first 30 days	18%	31%
Reoperation after first 30 days for bleeding	47%	60%
Local infection	28%	34%
Sepsis	18%	16%

Gender Analysis Conclusions

- Not all women were enrolled in the small BSA group
- All though the number of women are small, there is a signal of a higher stroke rate, reoperation after 30 days, and reoperation for being after 30 days in the women
- This observation should be prospectively studied

Statistical Evaluation

Chul Ahn, Ph.D.

Cardiovascular & Ophthalmic Device Branch

Division of Biostatistics

OSB/CDRH/FDA

Nov. 30, 2007

Outline

- OPC vs. Performance Goal
- Study Design
- Study Results
- Statistical Issue: Pool-ability
- Summary

OPC

- An objective performance criterion (OPC) is a fixed target with an appropriate delta based on sufficient data.
- The sponsor derived an OPC from historical data including their clinical trials for the target patient population with BSA $\geq 1.5\text{m}^2$, and proposed a value of 75%.
- Study goal: success rate $> \text{OPC}(75\%) - \text{delta}(10\%)$

Performance Goal

- Confusion about OPC (Is it 75% or 65%?)
- The FDA prefers using a **Performance Goal** because of limited data
- A performance goal (PG) is a fixed value to which the device's performance is compared to and which appears in the statistical hypothesis as a parameter value (here 65%).

Performance Goal (cont'd)

- A Performance Goal was developed by FDA in 2002 for the rate of survival to cardiac transplantation.
- It was developed based on six publications reporting on the majority of approved BTT devices where there exists a lower BSA limit of 1.5 m².

Some general comments about PG

- A PG should be developed for the **intended** patient population.
- The current patient cohort and the historical patient cohort that was used to develop the PG should be **comparable**.
- **It is neither superiority nor non-inferiority comparison!**
Appropriate claim: pre-specified performance goal is met.

Study Design

- Multi-center single-arm clinical trial compared to an OPC
- $H_0: P \leq \text{OPC} - 10\%$ vs. $H_a: P > \text{OPC} - 10\%$
where P is the proportion of successful patients in the intended patient population
- **Patient success:** Survival to cardiac transplantation **OR** 180 days of LVAD support while remaining transplant listed as a status 1A or 1B

Study Success Criterion

- $H_0: P \leq 65\%$ vs. $H_a: P > 65\%$
- Study success criterion:
Lower bound of one-sided 95% C.I. $> 65\%$

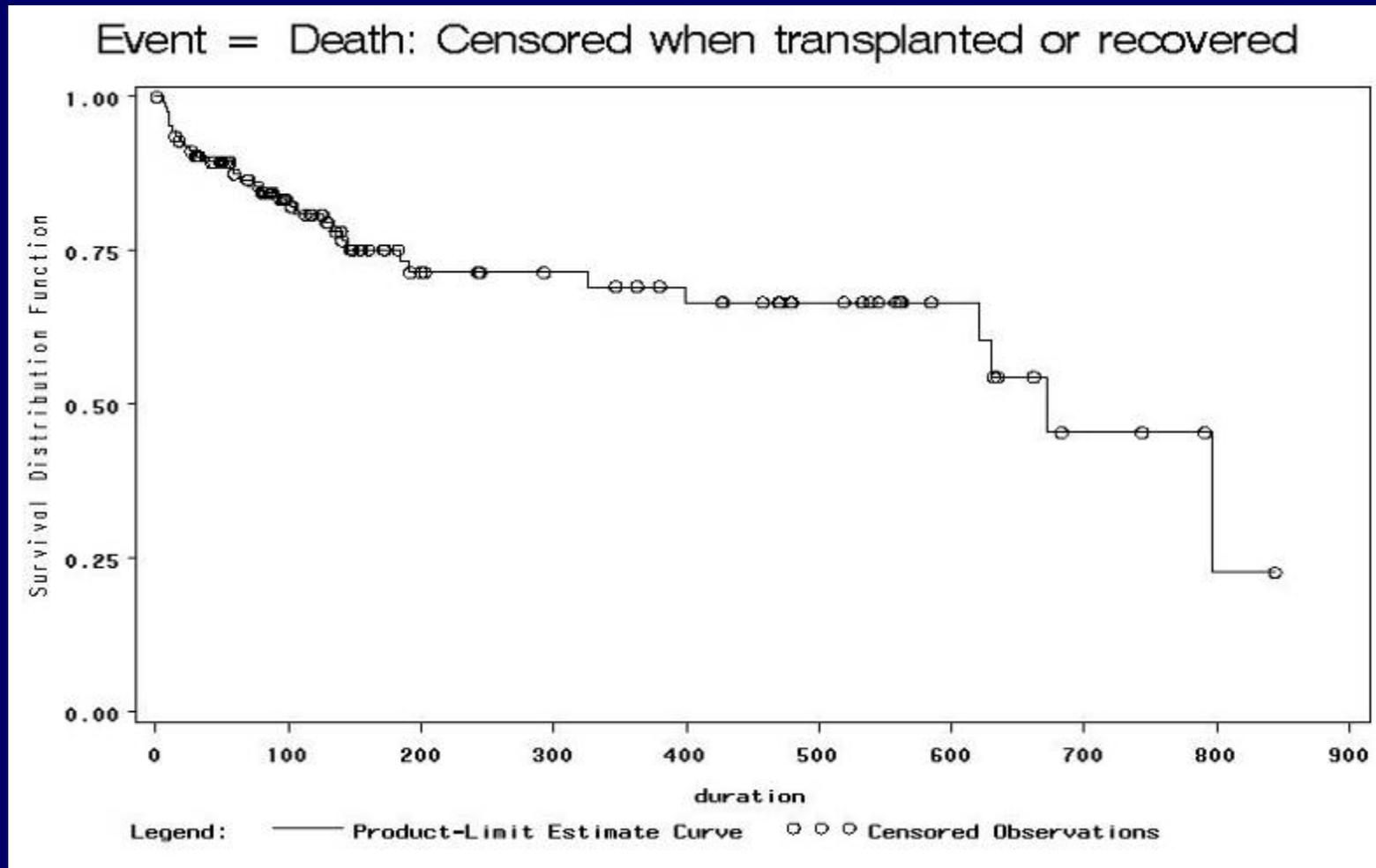
Secondary endpoints

No statistical hypotheses were specified for the secondary endpoints, so any statistical claims regarding secondary endpoints would be problematic.

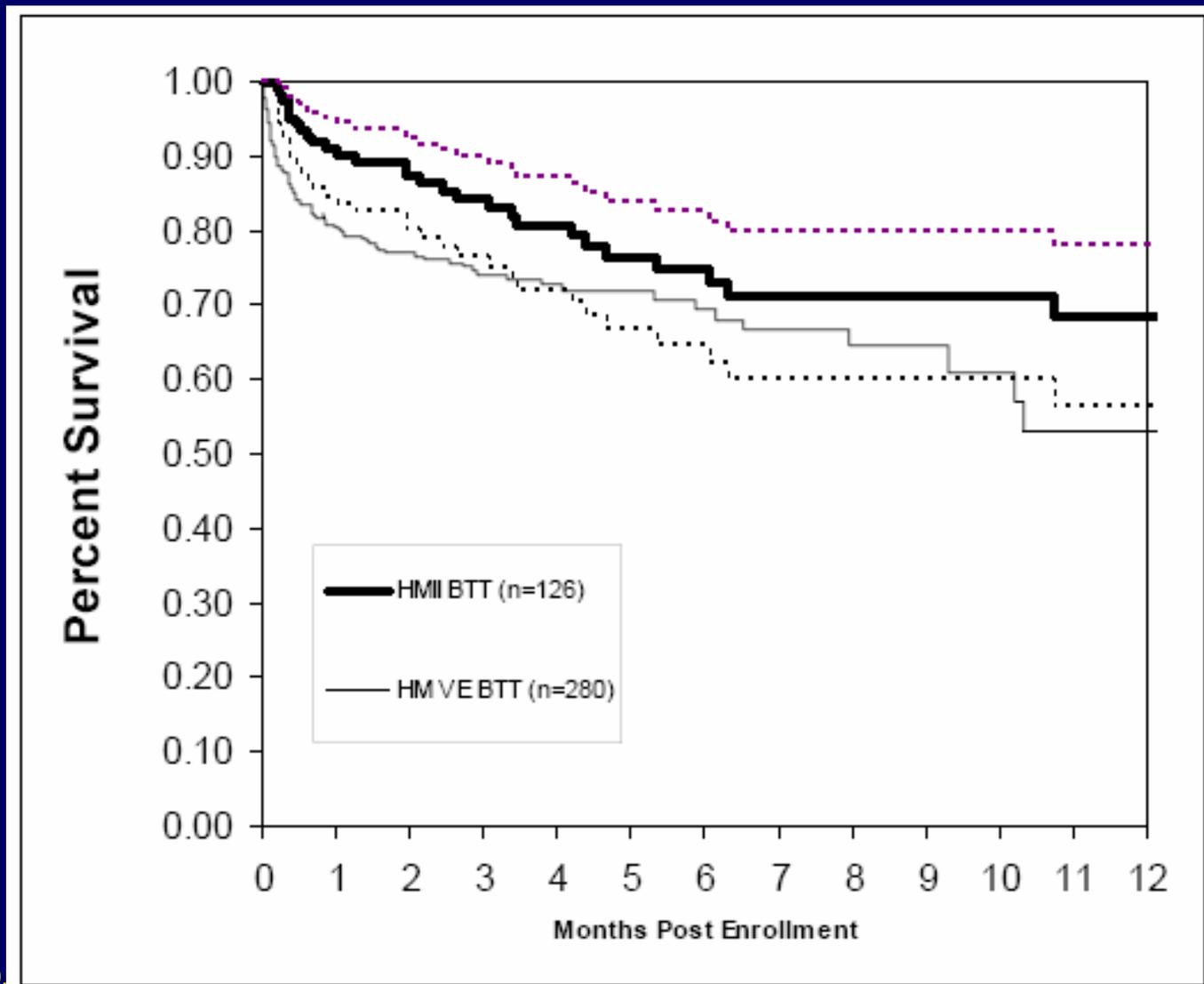
Primary Study Cohort Results

- N = 126 (BSA ≥ 1.5 m²)
- 89 successes (70.6%)
 - 72 – transplanted
 - 4 – recovered
 - 13 – supported 180 days and Status 1A or 1B
- Lower bound of one-sided 95% C.I. = 64.0%
→ The study failed regarding the primary endpoint

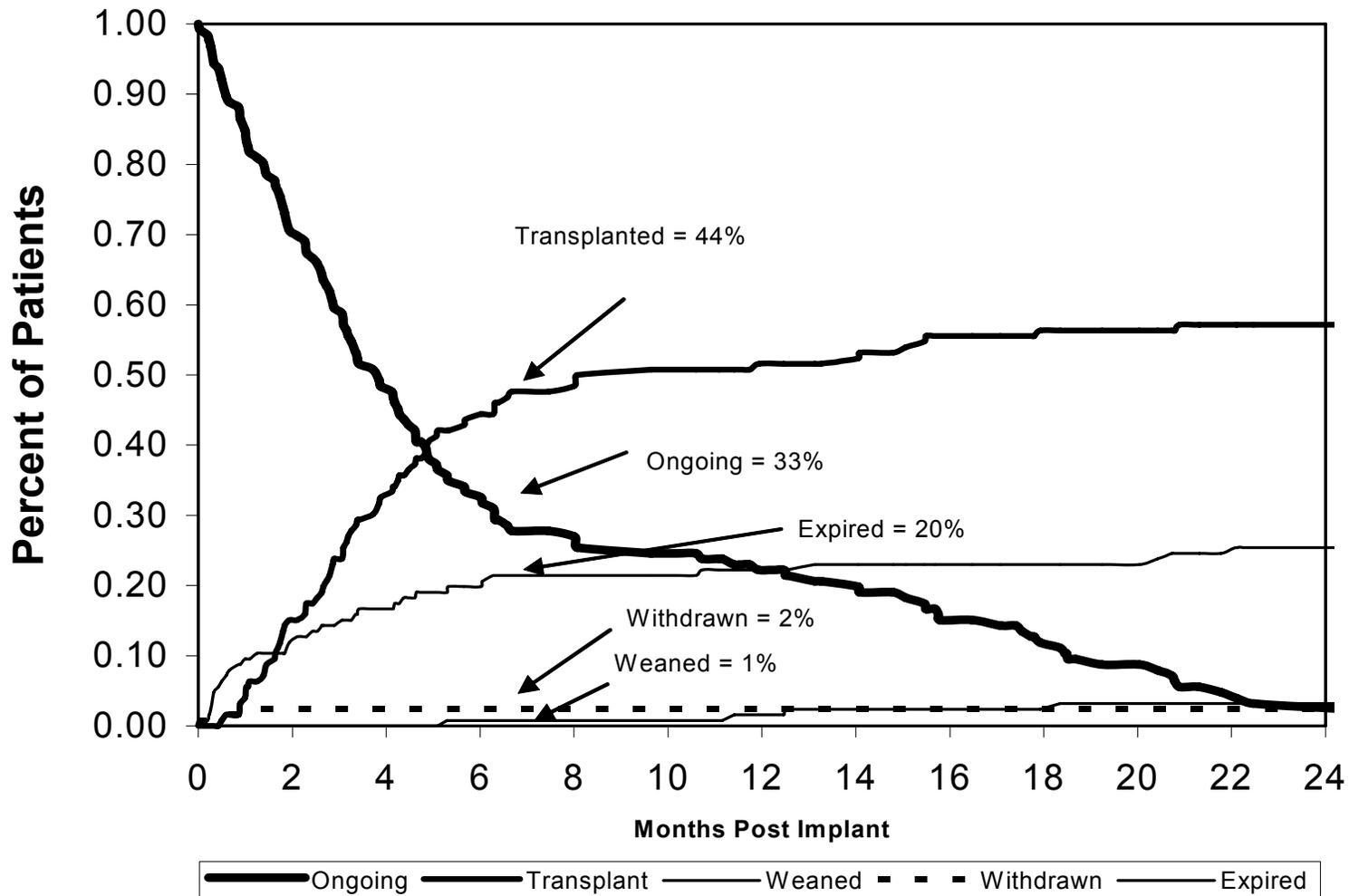
Kaplan Meier Curve for Primary Study Cohort



HeartMate II vs. HeartMate VE



Competing Outcomes Graph for Primary Study Cohort



Continued Access Protocol Results

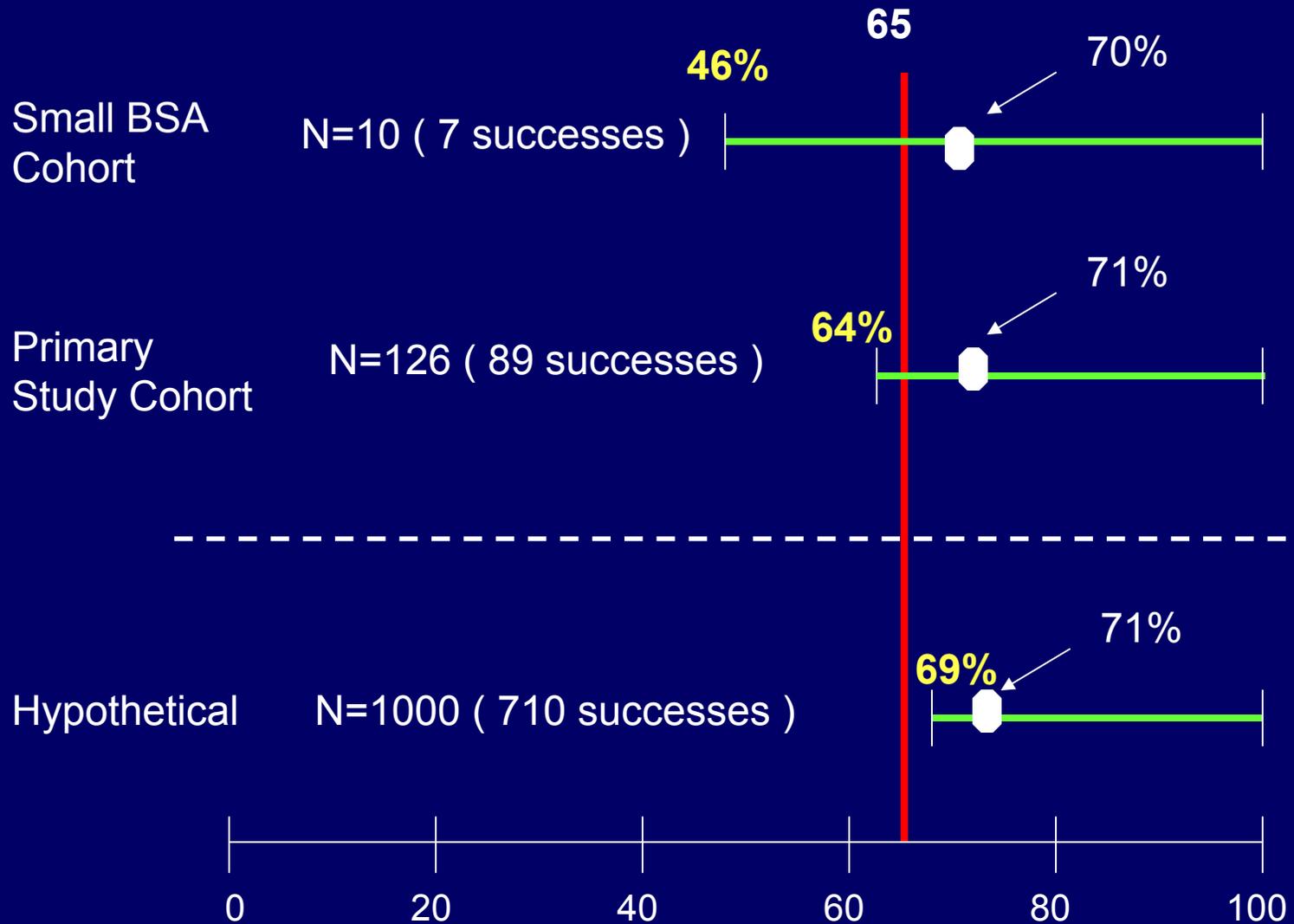
- N = 58 evaluable among 138 CAP patients
- 38 successes (65.5%)
 - 26 – transplanted
 - 1 – recovered
 - 11 – supported 180 days and Status 1A or 1B
- Lower bound of one-sided 95% C.I. = 55.3%

Small BSA Cohort Results

($1.2 \text{ m}^2 \leq \text{BSA} < 1.5 \text{ m}^2$)

- N = 15
 - 7 patients enrolled in the Pivotal
 - 8 patients enrolled in the CAP
- N = 10 evaluable (7 from Pivotal and 3 from CAP)
- 7 successes - 5 from Pivotal and 2 from CAP (70%)
 - 6 – transplanted
 - 0 – recovered
 - 1 – supported 180 days and Status 1A or 1B
- Lower bound of one-sided 95% C.I. = **46.2%**

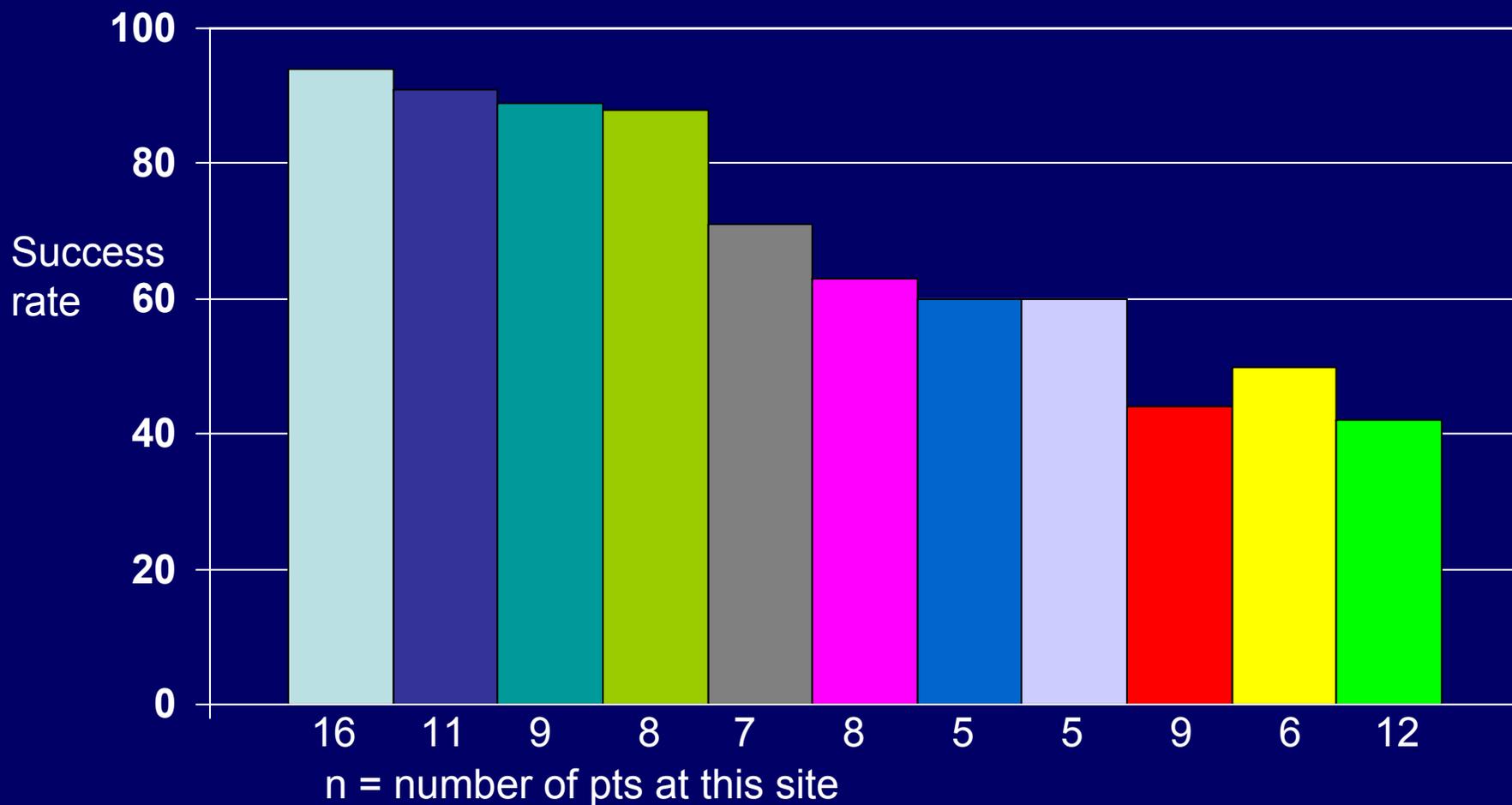
Effect of Sample Size on C.I.



Statistical issue: Poolability

Assessment of data poolability across investigational sites is challenging since the primary success rates are different among centers.

Primary Cohort Success Rate by Hospital (sites with 5 or more patients)



Primary Cohort Success Rate by Hospital

pts in each site success rate

3, 2, 2, 1, 1, 1, 1, 1	100.0%
16	93.8%
11	90.9%
9	88.9%
8	87.5%
7	71.4%
3, 3, 3, 3	66.7%
8	62.5%
5	60.0%
5	60.0%
9	44.4%
6	50.0%
12	41.7%
4	25.0%
1, 1	0.0%

Test for Homogeneity of Success Rates

$$H_0: P_1 = P_2 = \dots = P_{26}$$

H_1 : At least one differs

P-value = 0.0683 from Fisher's Exact Test
(0.0246 after deleting those less than 5 patients)

It suggests that the success rates may be different across the investigational sites.

Random effects hierarchical model

- Treat the success rate of each site as random effects arising from a common distribution
- Interested in the mean of this common distribution
- The 5% point of the distribution of this mean is 61.9%, which is slightly smaller than the lower bound of the C.I. (64%)

Mean	S.D.	5.0%	Median	95.0%
0.7015	0.04843	0.619	0.7041	0.7769

Statistical Summary

- The study failed regarding the primary endpoint.
- There is not enough information to draw a statistical conclusion of this device for patients with BSA less than 1.5 m².
- There is a statistical concern for data pooling across investigational sites and this may be due to unknown covariates.



Issues to Consider for a Post-Approval Study

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Disclaimer

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness.
- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Need for Post-Approval Studies in General

- Gather postmarket information
 - Longer-term performance
 - Real world community performance
 - Effectiveness of training programs
 - Sub-group performance
 - Rare adverse events
- Incorporate panel recommendations

Overview of Sponsor's Proposed PAS Protocol

Study Design	Prospective one armed observational registry study
Population	INTERMACS Registry patients receiving the HeartMate II Left Ventricular Assist System for bridge to transplant indication
Sample Size	78
Hypothesis	One sided lower bound for the 95% confidence interval for the success rate will be 60% or above
Follow-up	Discharge, 1 week, 1 mo., 3 mo., 6 mo.
Primary Endpoint	Successfully transplanted, weaned, or supported for 180 days
Secondary Endpoints	Adverse events, malfunction or failure, QOL, reoperations, rehospitalizations, neurocognitive

INTERMACS Registry

- Sponsors: NHLBI, CMS, FDA, others
- Purpose: Improve pt. evaluation & Rx
- Current status
 - 81 transplant centers
 - 489 patients as of November 9, 2007
 - Approximately 100-200 BTT patients may receive HeartMate II

PAS Issues for Panel Discussion

1) Basic study design

- Need for control group
- Appropriate length of follow-up

PAS Issues for Panel Discussion

2) Subgroup analysis by gender

- Women have smaller BSA
- Higher rate of local vascular complication after cardiac catheterization
- Higher rate of some adverse events in pivotal trial

PAS Issues for Panel Discussion

3) Adequacy of success criteria

- Limitations of performance goals
- Success criteria less than in pivotal study
- No mention of patient status at 180 days

PAS Issues for Panel Discussion

- 4) Assessment of cognitive function
 - Sponsor proposes only the Trail Making Part B Test
 - Question adequacy of Trail Making Part B test to assess neurocognitive function