



# **Edwards SAPIEN Transcatheter Heart Valve Model 9000 and RetroFlex 3 Delivery System**

## **FDA Review of P100041**

**Lisa Kennell**

Division of Cardiovascular Devices  
Office of Device Evaluation  
Food and Drug Administration

**Circulatory System Devices Panel Meeting  
July 20, 2011**

# FDA Team Presenters

**Lisa Kennell**

*Introduction and Pre-Clinical*

**Chenguang Wang, PhD**

*Statistical Summary*

**Julie Swain, MD**

*Clinical Summary*

**Mary Beth Ritchey, PhD**

*Post-Approval Study*

**Matthew Hillebrenner, MSE**

*Summary*



# Outline

- Regulatory History
- Proposed Indications for use
- Device Description
- Pre-Clinical Testing
- Overview of PARTNER study
- Statistical Review
- Clinical Review
- Post-Approval Study
- FDA Summary

# Regulatory History

- SAPIEN IDE Study G030069
  - *Pivotal PARTNER study began in 2007*
- Premarket Approval (PMA) Application
  - *PMA application received November 2010*
  - *Data “freeze” or “lock” date November 1, 2010*
- Ongoing Study (Continued Access)
  - *Currently approved for 1680 patients at 23 sites*

# Proposed Indications for Use

- The Edwards SAPIEN Transcatheter Heart Valve (THV) is indicated for use in the following clinical conditions:

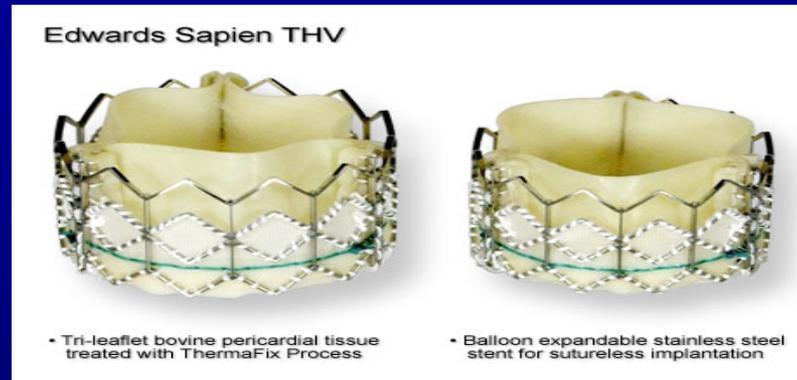
*The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23mm and 26mm and RetroFlex 3 Delivery System are indicated for transfemoral delivery in patients with severe aortic stenosis **who have been determined by a cardiac surgeon to be inoperable** for open aortic valve replacement and in whom **existing co-morbidities would not preclude the expected benefit** from correction of the aortic stenosis.*

# Proposed Indications for Use

(continued)

- Consistent with patient selection process used in the PARTNER study to define “inoperable” patient
  - Most important to have surgeon assess operability of patient
- Language added to improve patient selection process by identifying “inoperable” patients who are likely to benefit from this treatment option
  - Several patients enrolled in trial who may have been too sick to benefit from isolated treatment of severe aortic stenosis

# Device Description



- The Edwards SAPIEN THV
  - Heterologous (bovine) tissue sutured within a stainless steel stent
  - Aortic Sizes: 23 and 26 mm
  - Polyethylene terephthalate (PET) cuff
- RetroFlex 3 or RetroFlex delivery system available in sizes 20 and 23 mm for pre-dilating to ease crossing size 23 and 26 mm valve
- Sheath Set with Introducer, Sheath, and Loader with Cap
- A dilator kit



# FDA Pre-Clinical Review Team

- **Team Leader**
  - *Lisa Kennell*
- **Engineering**
  - *Changfu Wu PhD*
  - *Nandini Duraiswamy PhD*
  - *Sandy Stewart PhD*
  - *Stephen Retta MS*
  - *Albert Rodriguez*
- **Animal Study**
  - *Michael John, MPH*
- **Patient Labeling Review**
  - *David Windt, MPH*
- **MRI**
  - *Terry Woods PhD*
  - *Wolfgang Kainz PhD*
- **Microbiology**
  - *Lisa Kennell BS*
- **Bio-Research Monitoring**
  - *Adam Donat MS*
- **Manufacturing**
  - *Andrea P. Artman MS*
  - *Daniel Walter*

# Pre-Clinical Testing

- Biocompatibility
- Sterility & Packaging
- Magnetic Resonance Imaging (MRI)
- Delivery system
- Manufacturing
- Bio-research monitoring
- Corrosion resistance evaluation of the valve stent
- Fatigue evaluation of the valve stent
- Hydrodynamic and durability testing of the whole valve
- Valve migration potential evaluation
- *In Vivo* sheep studies

**No further concerns about the majority of testing.**

**However, no testing was conducted on valve-in-valve implantation.**

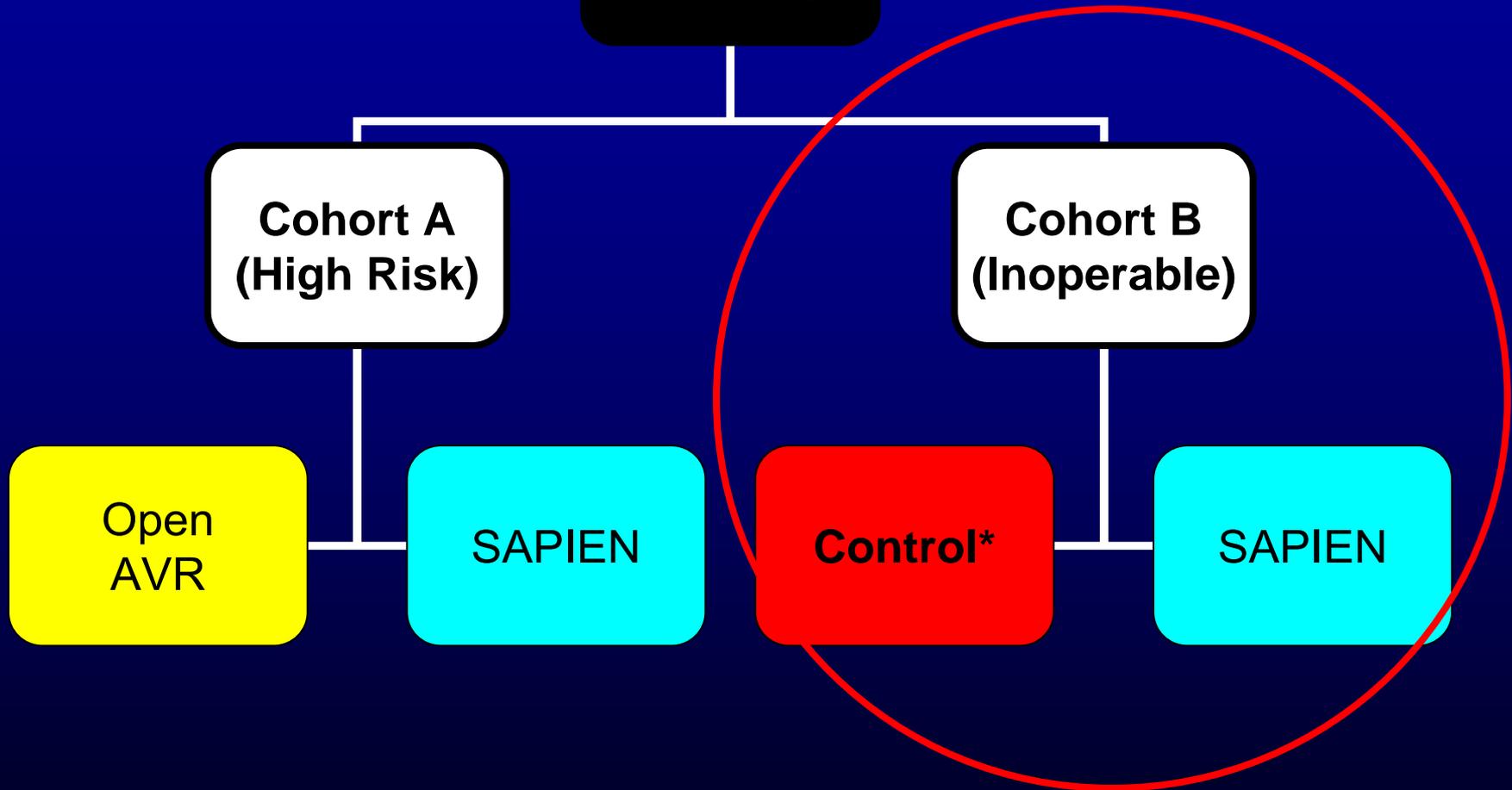
# Valve-in-Valve

- 4 cases of valve-in-valve in Cohort B study
- Many more cases outside of the U.S., as reported in the literature
- Different valve positions
  - Aortic, mitral, tricuspid, and pulmonic
- Different configurations
  - TAV-in-TAV
  - TAV-in-SAV
  - TAV-in-Ring

# Valve-in-Valve: Potential Risks

- Size mismatch
  - 2-3 sizes for current transcatheter valves vs. various sizes for surgically placed bioprosthetic valves
  - Impact on stable anchoring and uncompromised hemodynamic performance
- Valve migration/embolization
- Long term durability
- Fretting fatigue
- Galvanic corrosion
- Access to the coronary ostia

# PARTNER IDE Trial



CONTROL = BAV, Open AVR, Apico-aortic conduit, TAVR, and/or optimum medical therapy

# Study Endpoints

- Primary endpoints of freedom from all cause death and composite of death and recurrent hospitalization were met
- FDA will focus mainly on totality of the data/key secondary endpoints

# Secondary Safety Endpoints

- Key secondary safety endpoints
  - Time from randomization to first MACCE (death, MI, all stroke, renal failure)
  - Serious adverse events
    - Neurological Events
    - Vascular Complications
    - Aortic Regurgitation

# Secondary Effectiveness Endpoints

- Key secondary effectiveness endpoints
  - Hospitalization
    - Total hospital days through one year
    - Days alive out of the hospital through 1 year
  - New York Heart Association (NYHA) functional classification
  - 6-Minute Walk Test
  - Effective Orifice Area



# **FDA Statistical Review of P100041**

**Chenguang Wang, PhD**

Cardiovascular and Ophthalmic Devices Branch  
Division of Biostatistics  
Office of Surveillance and Biometrics



# Outline

- 1. Study Design and Progression**
- 2. Patient Accountability**
- 3. Primary Endpoint Results**
- 4. Secondary Endpoint Results**
- 5. Summary**



# Study Design and Progression

- Design
  - Prospective, nonblinded, randomized, controlled, multi-center clinical trial
  - Calculated sample size 350 with estimated power 85%
- Enrollment
  - First enrollment 5/11/2007
  - 358 patients (179 Control, 179 SAPIEN) enrolled by 3/16/2009
  - 22 Centers (4 OUS)
- Final statistical analysis plan on 2/18/2010.
- Data cut-off date 11/1/2010
  - All events *after* the cut-off date *excluded*



# Patient Accountability

- Control
  - 5/179 (2.8%) withdrawals by the data cut-off date
  - 14/86 (16.3%) eligible patients missing one-year in-window visit
- SAPIEN
  - 1/179 (0.6%) withdrawal by the data cut-off date
  - 12/124 (9.7%) eligible patients missing one-year in-window visit
  - 9/179 (5.0%) did not receive the device

# Patient Demographics and Baseline Characteristics

- No statistically significant difference detected for the distributions of patient demographics and baseline characteristics between Control and SAPIEN.
- Potential clinically significant difference
  - Percentage numerically higher in Control:
    - coronary artery disease
    - previous MI
    - previous CABG
    - COPD
    - O<sub>2</sub> dependence
    - elevated creatinine
    - atrial fibrillation
  - Percentage numerically higher in SAPIEN:
    - peripheral vascular disease
    - extensively calcified aorta
    - chest-wall deformity



# Analysis Population

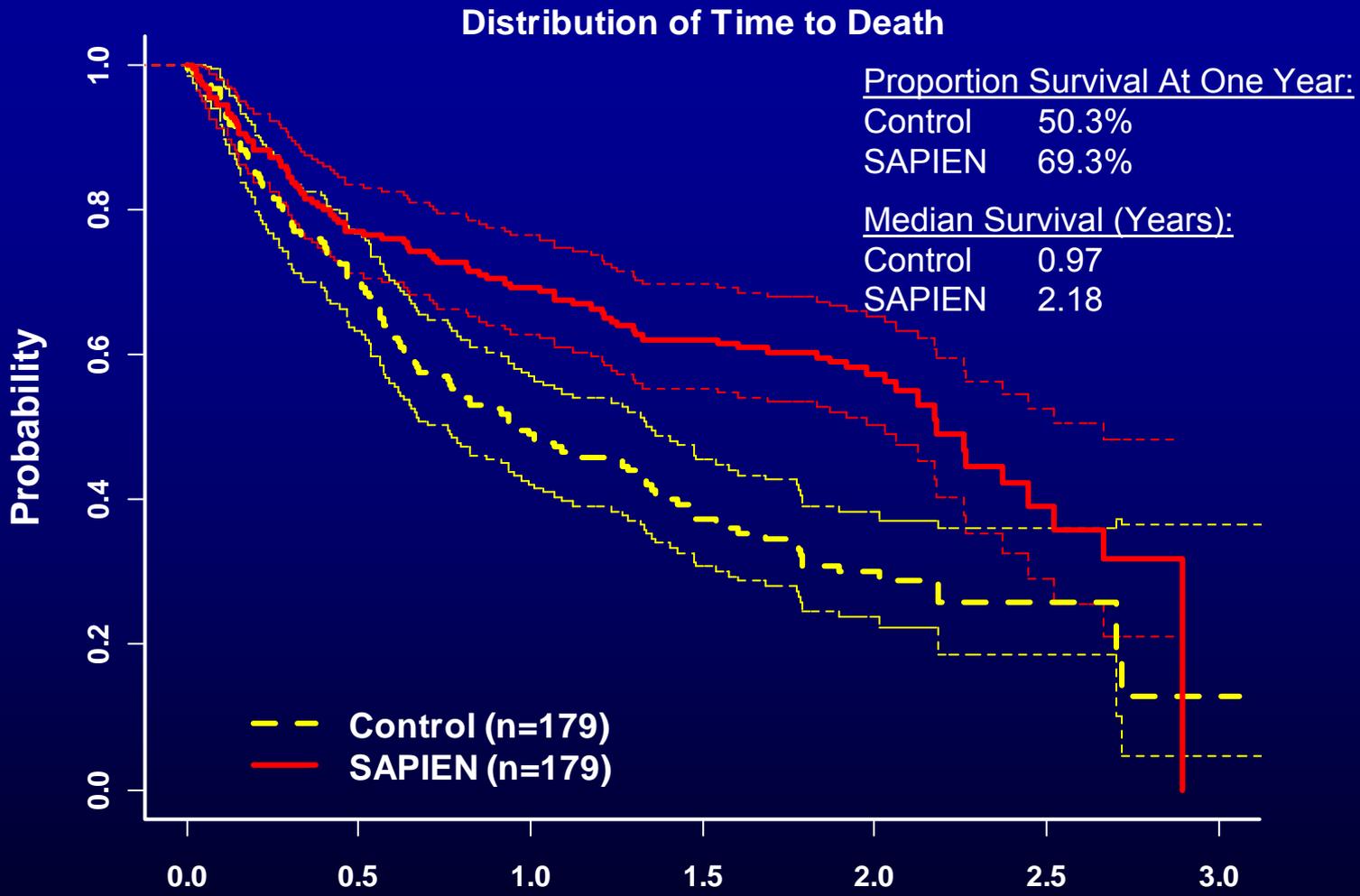
- Protocol specified analysis populations:
  - Intent-To-Treat (ITT)
    - All randomized patients
  - “As Treated” (AT)
    - AT Control: Randomized control patients and patients randomized to SAPIEN who did not receive the implant
    - AT SAPIEN: Randomized Treatment patients for whom the study valve implant procedure is begun
- The analyses of the primary and secondary endpoints based on the ITT population, which was pre-specified in the protocol, will be presented.



# Primary Safety and Effectiveness Endpoint

- *Definition*
  - *Freedom from death (over the duration of the trial)*
- Null and alternative hypotheses:
  - $H_0$ : Survival function of SAPIEN = Survival function of Control
  - $H_1$ : Survival function of SAPIEN  $\neq$  Survival function of Control
- Superiority test of SAPIEN over Control
- All-cause mortality significantly lower for SAPIEN. (log-rank test, two-sided p-value  $< 0.0001$ ).

# Primary Safety and Effectiveness Endpoint



	Number at Risk						
	0.0	0.5	1.0	1.5	2.0	2.5	3.0
Control	179	122	85	56	24	4	1
SAPIEN	179	138	124	103	61	13	0



## Co-primary Endpoint: Death and Re-hospitalization

- *Hierarchical composite of death and recurrent hospitalization*
- Endpoint proposed after the initiation of study
- Null and alternative hypotheses
  - $H_0$ : Neither survival nor the re-hospitalization is different
  - $H_1$ : At least one and possibly both components are different
- Finkelstein-Schoenfeld test
- Statistical significance achieved in favor of SAPIEN (two-sided p-value <0.0001)



# Finkelstein-Schoenfeld (FS) Method

- Non-parametric rank sum test where each patient is compared to every other patient in a pairwise manner.
- All patient pairs are compared first on survival if this comparison is possible. If not, patients are then compared on time to first recurrent hospitalization.



# Secondary Endpoint: MACCE

- *Definition:*
  - *Time from randomization to the first occurrence of a MACCE event (death, MI, all strokes and renal failure) within one year*
- MACCE beyond one year not included
- Nominal two-side p-value 0.0176 (log-rank test) favoring SAPIEN
- FDA clinical reviewer will discuss the MACCE components



# Secondary Endpoint: Hospitalization

- *Definition:*
  - *Total Hospital Days Through One Year*
    - Control Median: 8 days
    - SAPIEN Median: 12 days
    - Nominal two-sided p-value 0.019 (Bootstrap test)
- **Additional Analysis**
  - *Days Alive and Out of the Hospital Through One Year*
    - Proposed after the study was begun
    - Control Median: 233 days
    - SAPIEN Median: 348 days

# Secondary Endpoint: NYHA at One Year

	Missing	Dead	I	II	III	IV	Total
Control	<b>11</b>	<b>89</b>	2	29	37	11	179
SAPIEN	<b>7</b>	<b>55</b>	45	44	23	5	179
Total	<b>18</b>	<b>144</b>	47	73	60	16	358

- Sensitivity analyses regarding missing data conducted
- Results favored SAPIEN
- Possible systematic bias for nonblinded trials



## Secondary Endpoint: Six-Minute Walk Test at One Year

- Observed
  - Control:  $151 \pm 78$  meters
  - SAPIEN:  $216 \pm 132$  meters
- Missing
  - Control: 59/90 (66%)
  - SAPIEN: 68/124 (55%)
- Sensitivity analyses regarding missing data conducted
- Results indefinite
- Difficult to draw firm conclusion because of missing data



# Summary of FDA Statistical Review

- The study met its pre-specified primary endpoint
- This presentation highlights the primary and secondary endpoints with pre-specified hypotheses
- FDA clinical reviewer will discuss key effectiveness and safety issues

# **FDA Clinical Review of P100041**

**Julie A. Swain, MD**  
Cardiovascular Surgeon

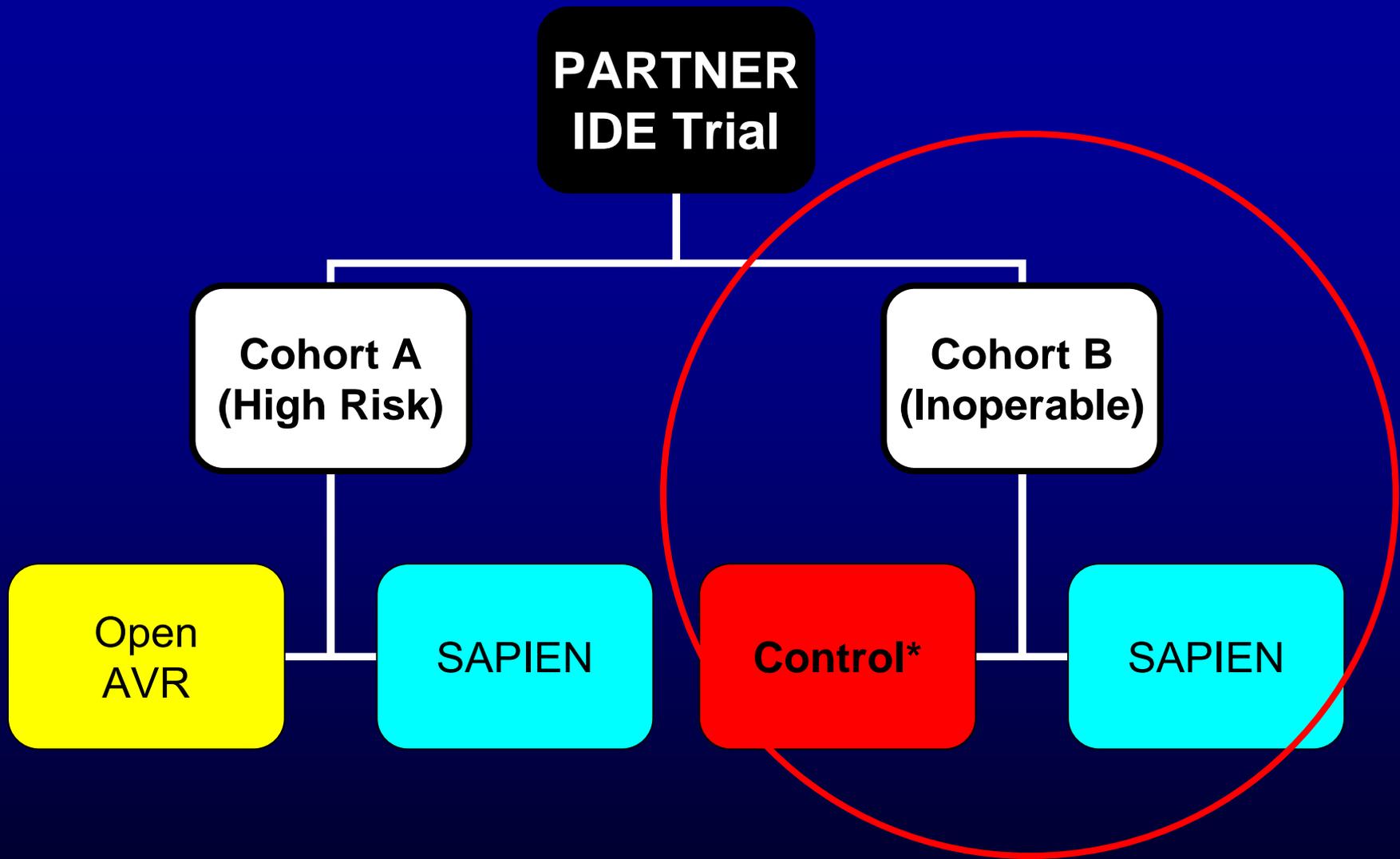
Circulatory Support & Prosthetics Branch  
Division of Cardiovascular Devices  
Office of Device Evaluation



# SAPIEN Clinical Experience



- 1<sup>st</sup> US Feasibility
- 2<sup>nd</sup> US Feasibility
- Roll-in Registry IDE Trial
- **Randomized, Controlled IDE Trial**
- Randomized Continued Access Registry
- Continued Access Registry
  
- European data 7000+ patients
  - EuroScore as inclusion (invalid for isolated valves, overpredicts mortality 3-7 times)
  - Surgeon determination of inoperability not required



CONTROL = BAV, Open AVR, Apico-aortic conduit, TAVR, and/or optimum medical therapy

# Randomized IDE Trial Cohort B

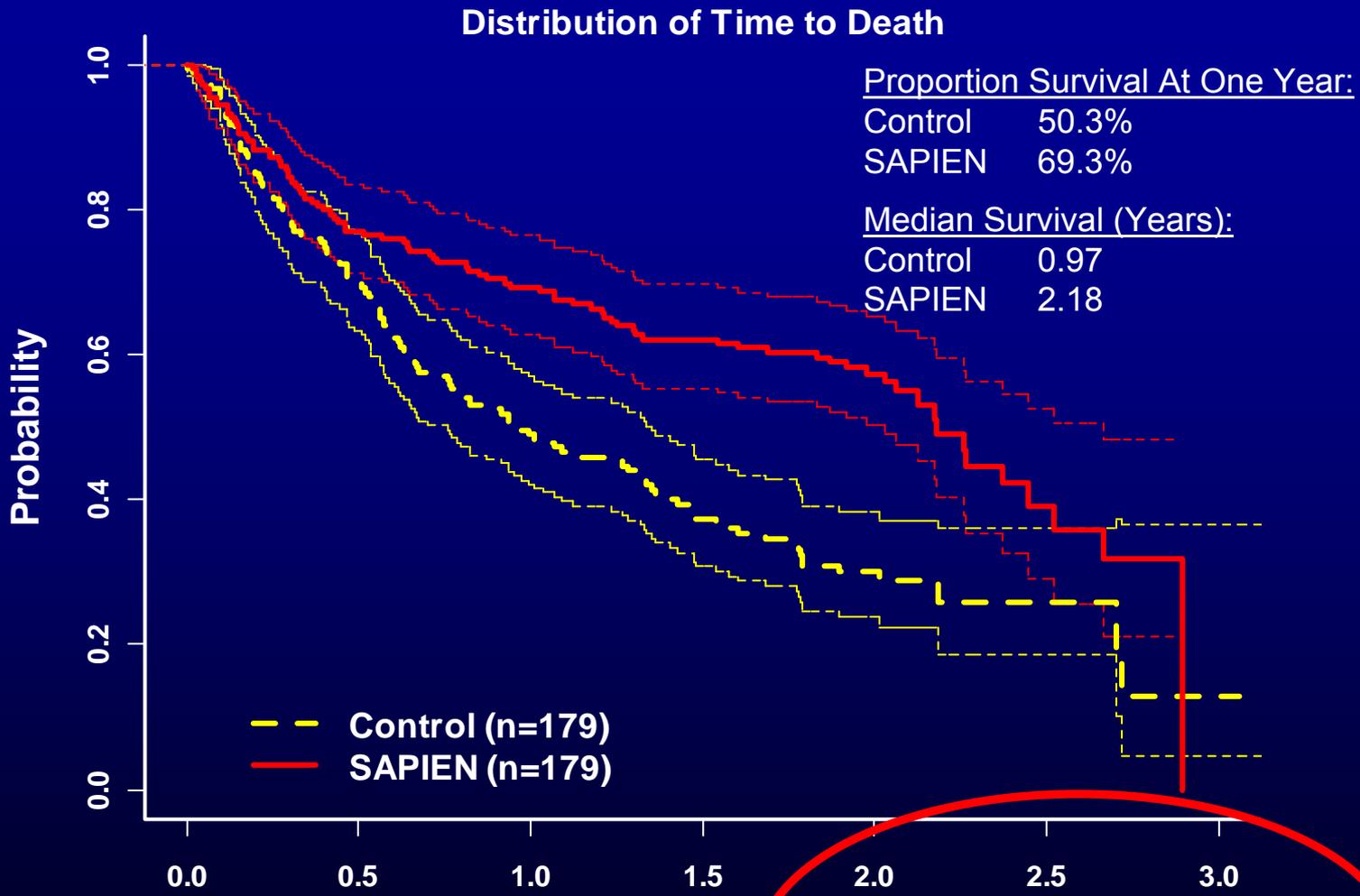


- Transfemoral TAVR vs “standard” treatment
- Inoperable, anatomically eligible for transfemoral
  - Transapical studied in Cohort A arm only
- “Inoperable” does not necessarily mean “short-lived”
- FDA asked that transapical be included – Sponsor declined (Limits population for labeling)

# Key Procedural Data

<b>Variable</b>	<b>Mean (min-max)</b>
<b>Total Procedure Time (min)</b>	<b>262 (139 – 616)</b>
<b>Fluoro time (min)</b>	<b>29 (10 – 68)</b>
<b>Contrast Vol (ml)</b>	<b>132 (10 – 450)</b>
<b>Gen. Anesthesia</b>	<b>100% of patients</b>
<b>Procedure Success (device success, no MACCE &lt;30d)</b>	<b>71.8%</b>

# Primary Safety and Effectiveness Endpoint

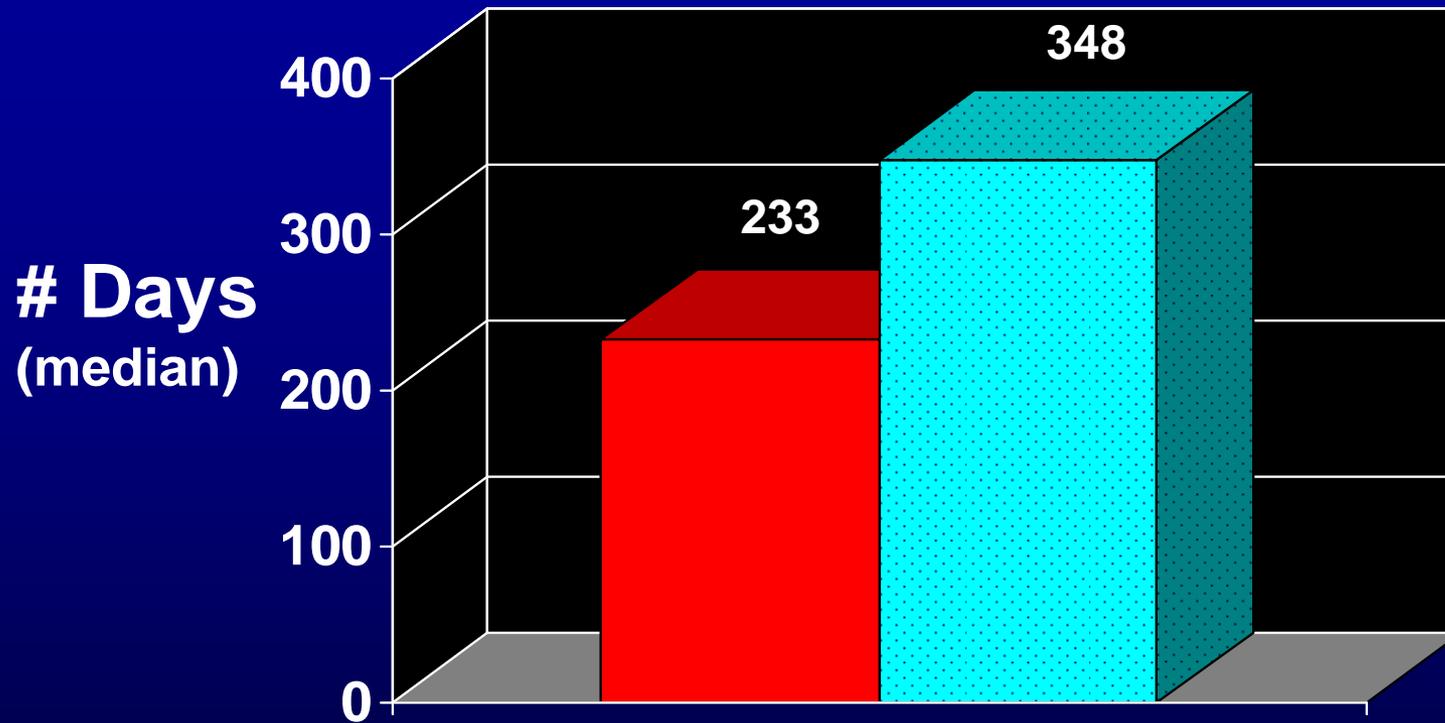


	Years						
Number at Risk	0.0	0.5	1.0	1.5	2.0	2.5	3.0
Control	179	122	85	56	24	4	1
SAPIEN	179	138	124	103	61	13	0

# Co-Primary Endpoint (free from mortality/hospitalization)

- Interpretation complicated by possible assessment bias, treatment bias, and placebo effect in this unblinded trial

	<b>0-1 years</b> (# at risk)		<b>1-2 years</b> (# at risk)		<b>2-3 years</b> (# at risk)	
	<b>Con</b>	<b>TEST</b>	<b>CON</b>	<b>TEST</b>	<b>CON</b>	<b>TEST</b>
	.282	.564	.120	.454	.090	0
	(179)	(179)	(49)	(101)	(10)	(49)



**Days Alive Out of Acute Care Hospital in 1 year**

 Control

 SAPIEN



# Other Secondary Endpoints



## NYHA

- subject to placebo effect, assessment bias
- interpretation of results in an unblinded trial is difficult

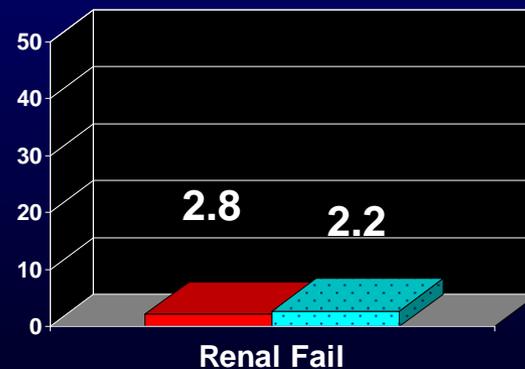
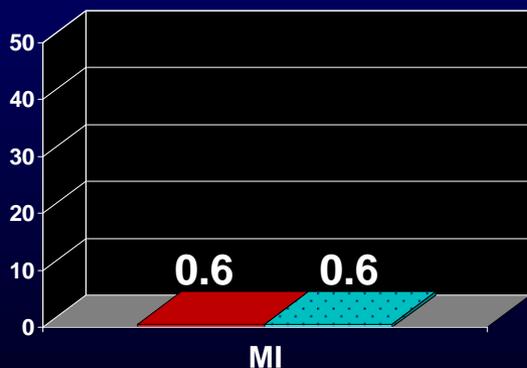
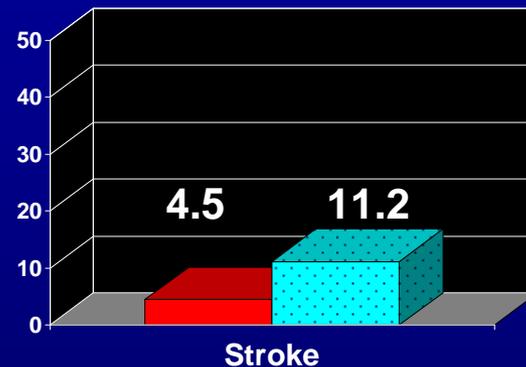
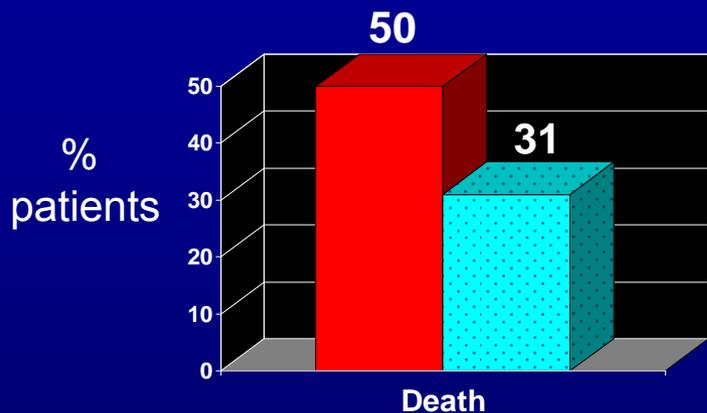
## 6 Minute Walk Test

- subject to placebo effect
- >50% missing data - interpretation impossible



# MACCE at 1 year

(all cause death, all stroke, MI, renal failure)

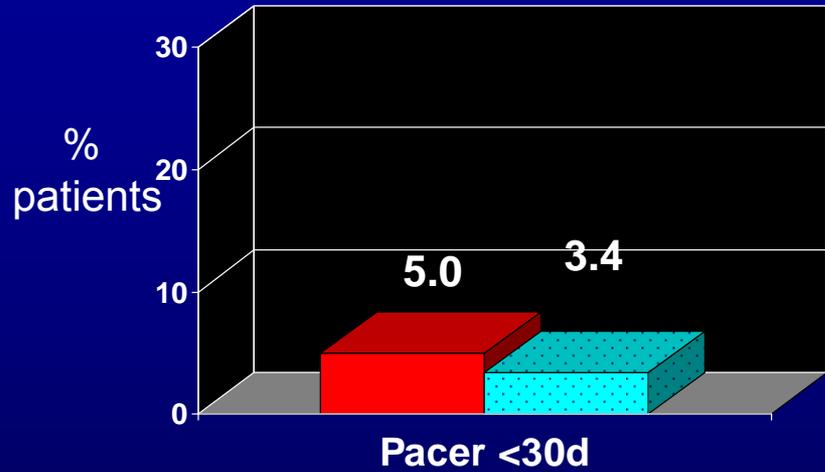


 Control

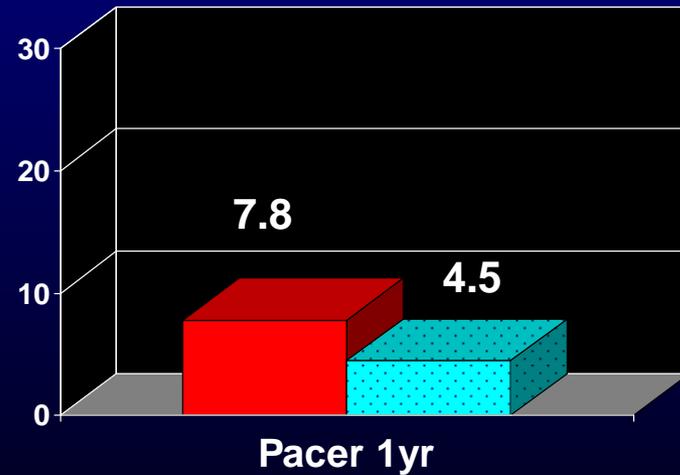
 SAPIEN

Note: Vascular complications not included

# New Pacemaker



% patients



Control SAPIEN

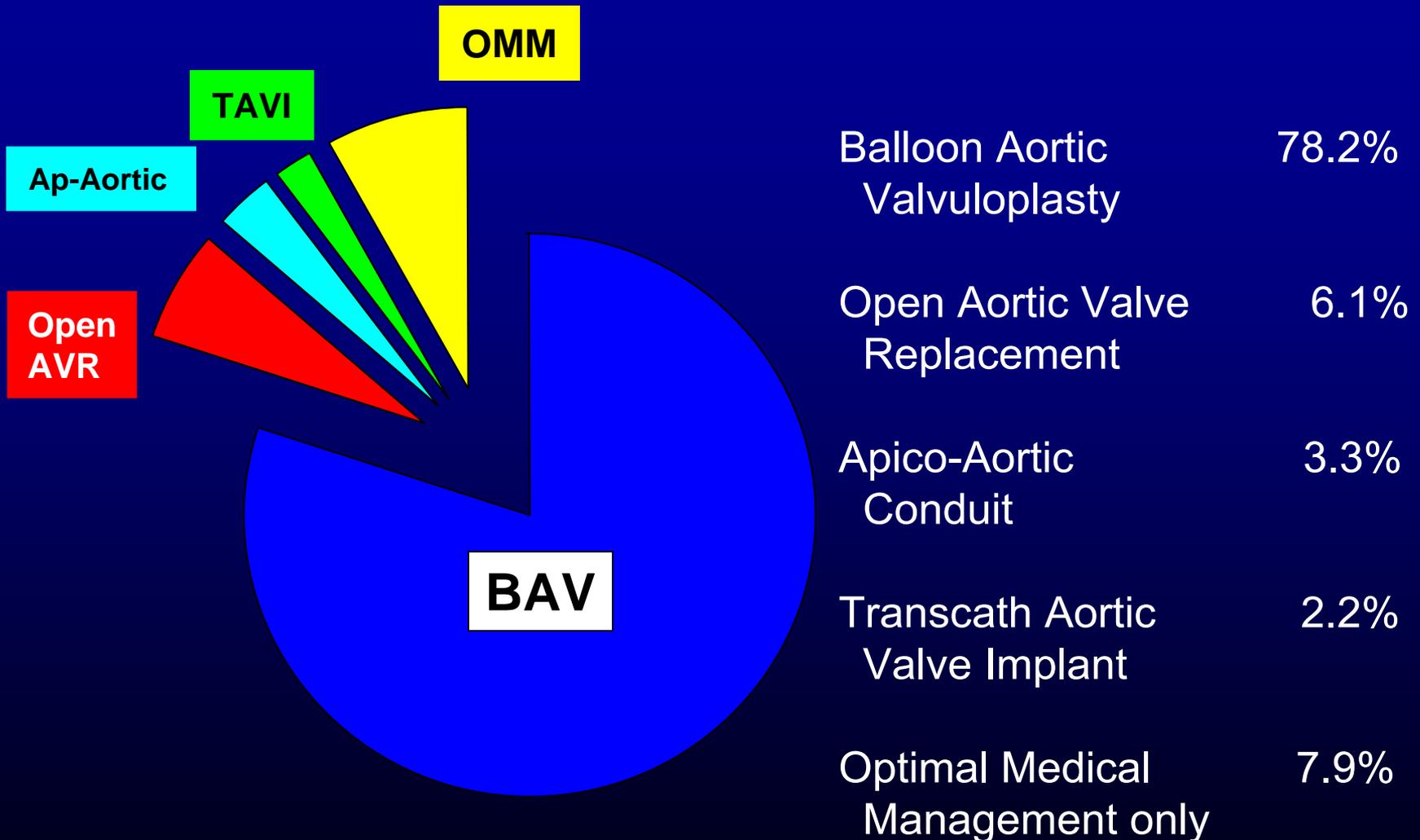


# Important Considerations



1. Heterogeneity of control
2. *Post hoc* adverse event definitions
3. Neurological damage
4. Vascular injury
5. Aortic Insufficiency
6. Patient selection

# Control “Standard” Therapy





# Implications of Control Heterogeneity



- Superiority is to “no SAPIEN implant”
- Control treatment selection not protocolized, possible selection bias in determining control treatment
- Not powered to compare SAPIEN with individual treatments - No proof of superiority to:
  - BAV
  - medical therapy
  - open AVR
  - Apico-aortic conduit

# Important Considerations



1. Heterogeneity of control
- 2. *Post hoc* adverse event definitions**
3. Neurological damage
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# Adverse Event Definitions

- FDA/Sponsor defined adverse events prior to start, FDA will use these for labeling
- Data analyzed, results known, then CEC was asked to redefine some adverse events (stroke, vascular), FDA not informed
- CEC Letter:  
*“The sponsor, Executive Committee and the PARTNER CEC agree that this adjudication is an **adjunctive process** to the primary adjudication process for PARTNER. This review is occurring **after the unblinded assessment** has been completed and as such there is **clear variation from the primary adjudication process** for PARTNER as described in the CEC Charter.”*

# Important Considerations

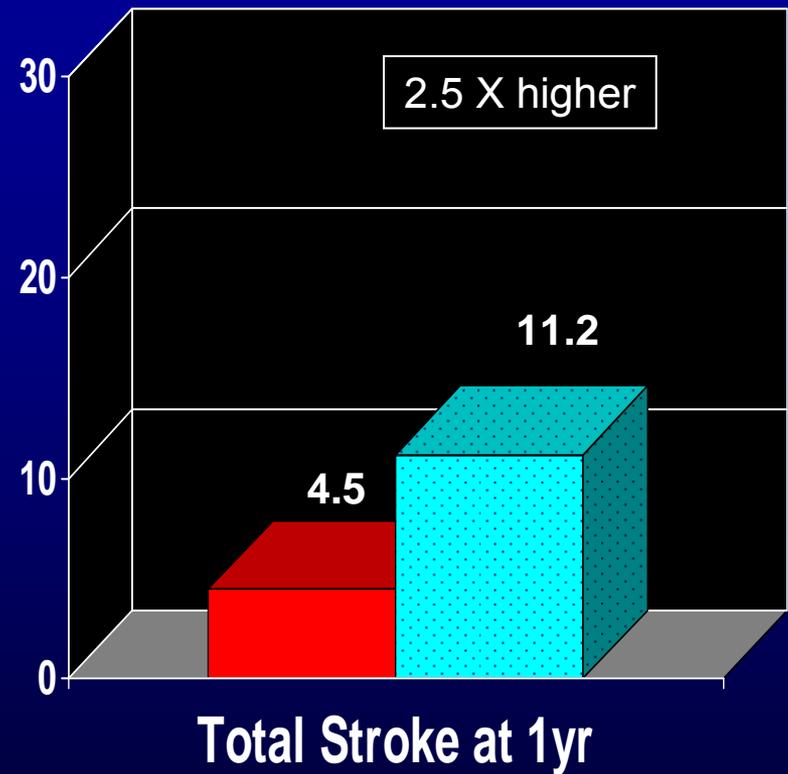
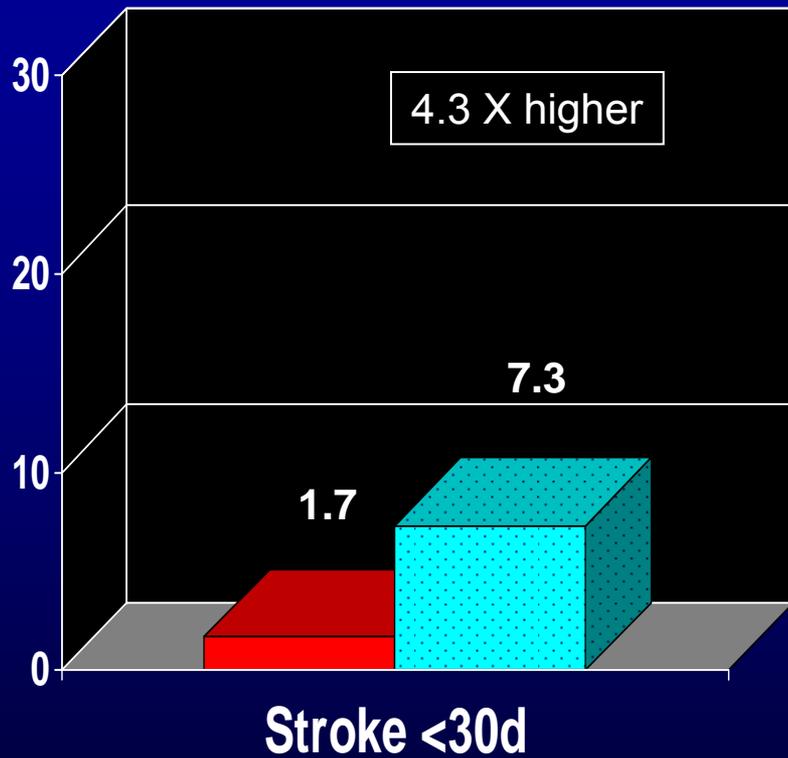


1. Heterogeneity of control
2. *Post hoc* adverse event definitions
- 3. Neurological damage**
4. Vascular injury
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# Definition of Stroke and MACCE

- Prespecified Definition of Stroke:
  - A neurological deficit lasting  $\geq 24$  hours, or lasting  $< 24$  hours with a brain imaging study showing infarction
- *Post hoc* “adjunctive” definition uses Modified Rankin Score for disability (major vs minor)
  - No patient had a Modified Rankin assessment
  - Sponsor agrees that retrospective Rankin is not validated
  - Stroke patients poor at self-evaluation
- Prespecified definition of MACCE included ALL stroke

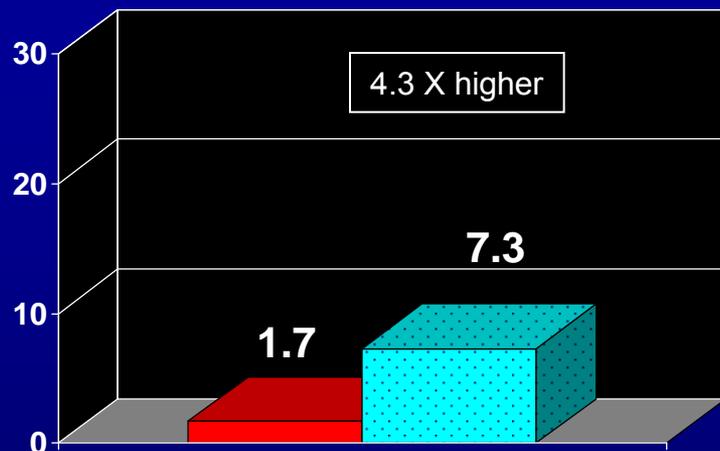
# Stroke (% patients)



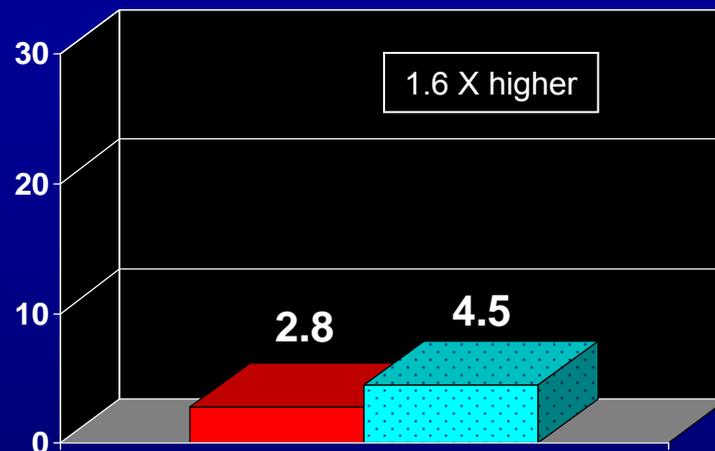
Note: No standardized anticoagulation/antiplatelet regimen

Control SAPIEN

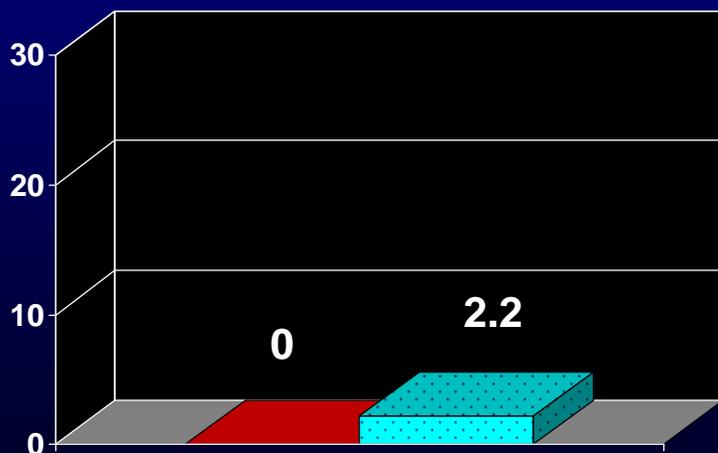
# Neurological Events (Stroke + TIA, % pts)



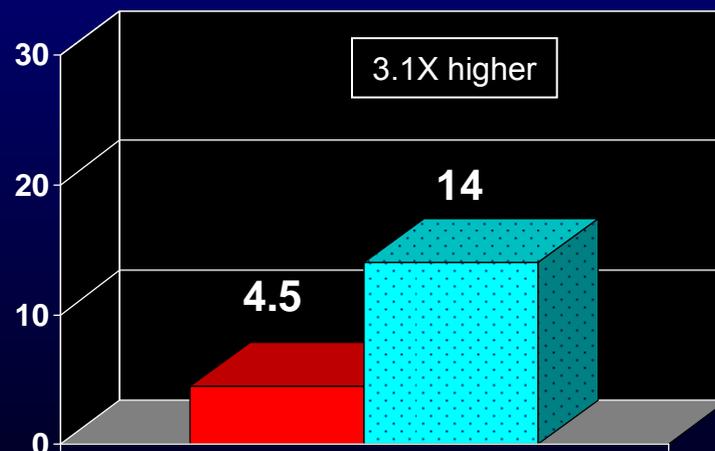
Neuro Events <30d



Neuro Events 30d - 1yr



Neuro Events >1yr



Neuro Events Total Study

Control SAPIEN

# Neurological Events

<b>Neurological Event</b>	<b>Control # events</b>	<b>SAPIEN # events</b>
Ischemic/unclassified stroke	7	16
TIA	0	3 (2pts)
Intracranial Hemorrhage	0	3
Hemorrhagic	1	3
<b>Total Events</b>	<b>8</b>	<b>25</b>

# Control Neuro Events



- 7 ischemic/unclassified strokes:
  - 1 after open AVR
  - 4 after BAV (5 days, 2 weeks, 2 months, 6 months)
  - 2 medical management (day of random, 3 days after random)
- One hemorrhagic stroke 8 months after BAV
- No intracranial hemorrhages
- No TIAs



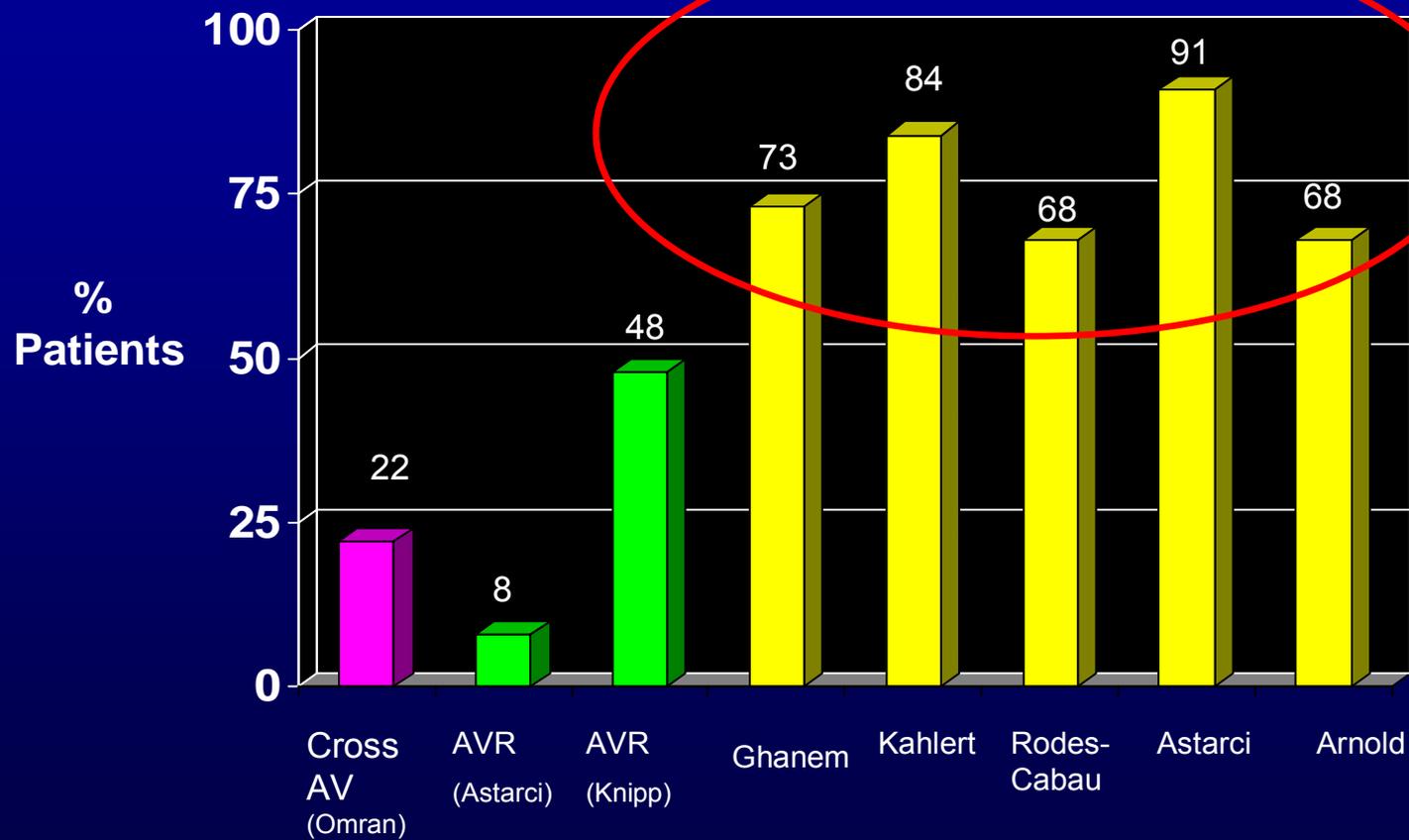
# SAPIEN Neuro Events

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- 16 ischemic/unclassified strokes:
  - 1 after randomization before SAPIEN
  - 10/16 were recognized within 6 days of SAPIEN implantation or attempted implantation
  - 2/16 occurred from 23-180 days (23, 75 days)
  - 3/16 occurred late (361, 650, 875 days)
- 3 hemorrhagic strokes (2, 39, and 120 days)
- 3 intracranial hemorrhages (51, 136, 151 days)
- 3 TIAs in 2 patients (143 days; 386/831 days)



# DW-MRI Lesions



# Cerebral Infarction after TAVI

- ~ 60% scans not done (death, complications, refusal, etc.)
- Limitations in assessment of stroke, no long-term assessment
- Possible mechanisms of injury:
  - catheter in arch
  - Balloon valvuloplasty
  - TAVI expansion
  - crossing stenotic AV
  - TAVI positioning
  - Corrective manipulation

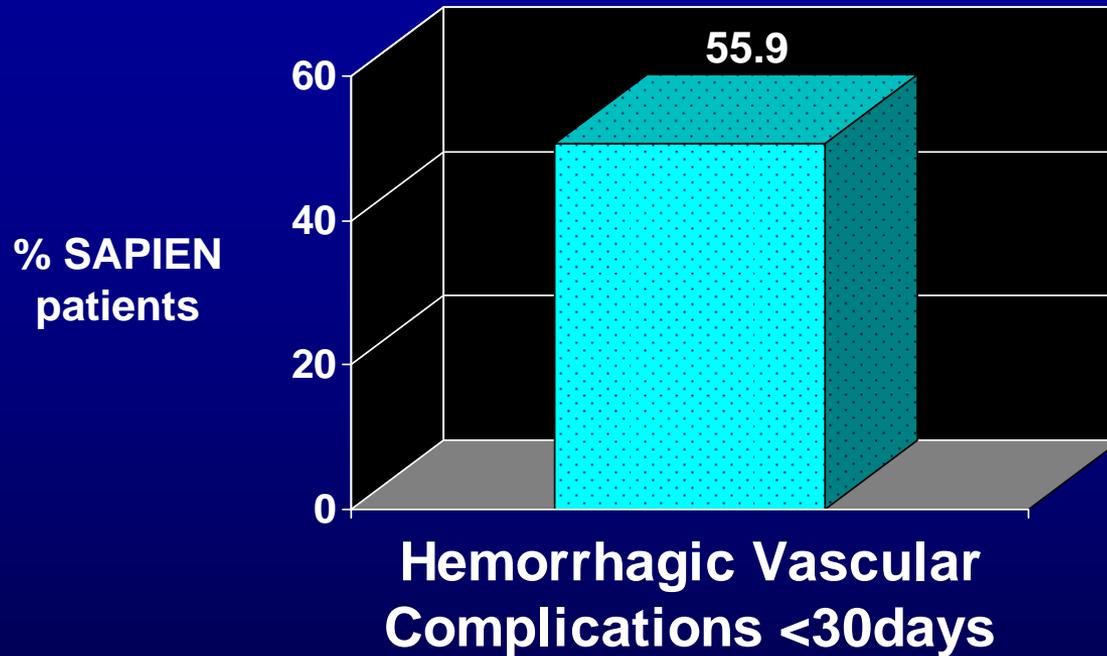
Future TAVI IDE studies – protocolized neurological assessment by neurologists in at least 50% of patients

# Important Considerations



1. Heterogeneity of control
2. *Post hoc* adverse event definitions
3. Neurological damage
- 4. Vascular injury**
5. Aortic Insufficiency
6. Patient selection

# Hemorrhagic Vascular Complications



1. Hematoma at access site >5 cm
2. False aneurysm
3. Arterio-venous fistula
4. Retroperitoneal bleeding
5. Peripheral ischemia/nerve injury
6. transfusion for cath complication.
7. Vascular surgical repair

# Selected Vascular Complications (SAPIEN)

<b>Acute Vascular Complications</b>	<b># Patients</b>
Aortic Dissection	1
Iliac artery/distal aortic	17
Femoral artery	13
Pseudoaneurysm	2
Hematoma	6
Unknown injury	2

FDA seeking Panel input on training program to minimize this complication

# Important Considerations



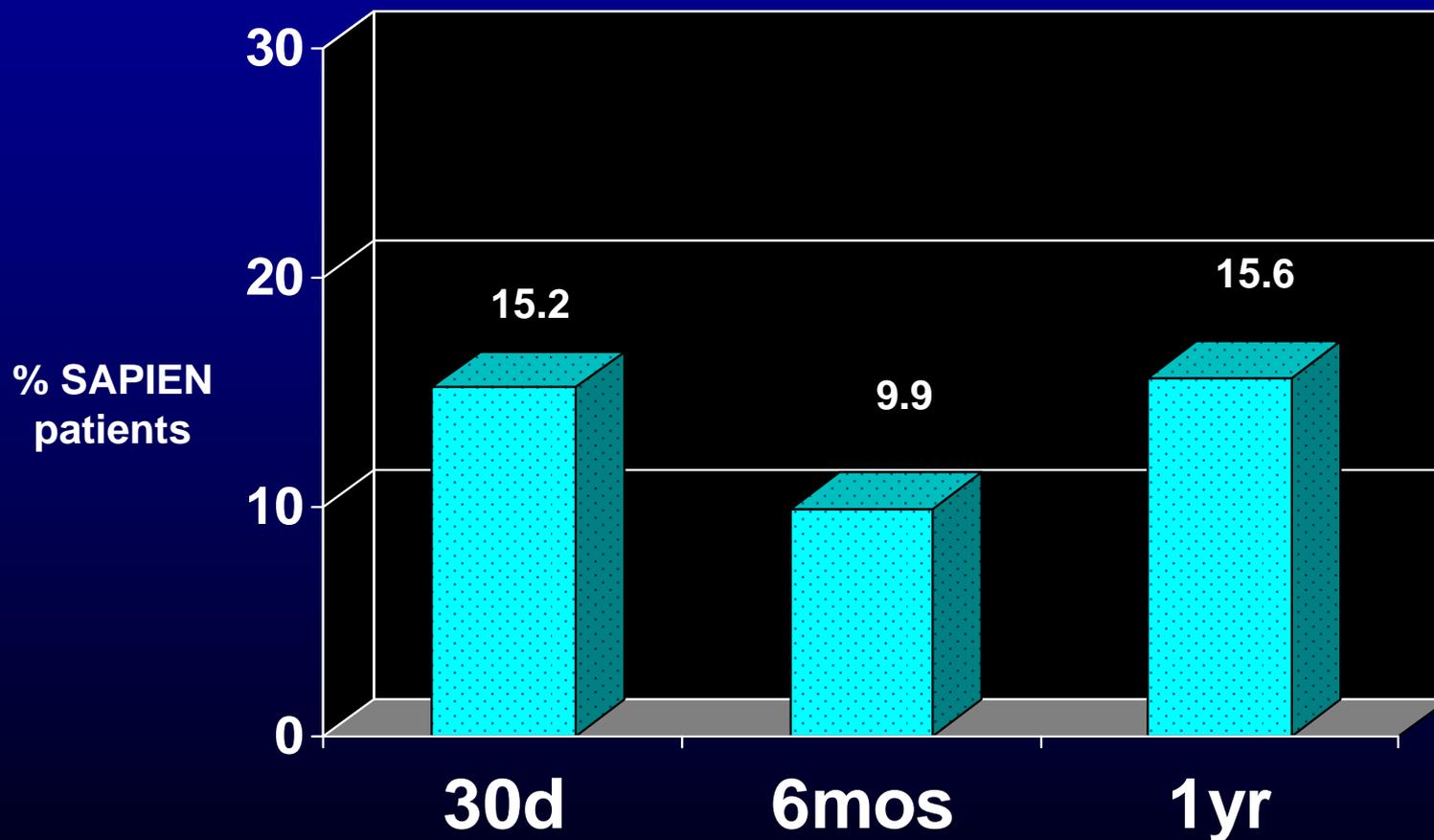
1. Heterogeneity of control
2. *Post hoc* adverse event definitions
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4. Vascular injury
- 5. Aortic Insufficiency**
6. Patient selection

# Aortic Regurgitation (ACC/AHA Guidelines 2006)

	Aortic Regurgitation		
	Mild	Moderate	Severe
<b>Qualitative</b>			
Angiographic grade	1+	2+	3-4+
Color Doppler jet width	Central jet, width less than 25% of LVOT	Greater than mild but no signs of severe AR	Central jet, width greater than 65% LVOT
Doppler vena contracta width (cm)	Less than 0.3	0.3-0.6	Greater than 0.6
<b>Quantitative (cath or echo)</b>			
Regurgitant volume (ml per beat)	Less than 30	30-59	Greater than or equal to 60
Regurgitant fraction (%)	Less than 30	30-49	Greater than or equal to 50
Regurgitant orifice area (cm <sup>2</sup> )	Less than 0.10	0.10-0.29	Greater than or equal to 0.30
<b>Additional essential criteria</b>			
Left ventricular size			Increased

# SAPIEN Aortic Regurgitation

Moderate (2+) or Greater  
Central + Paravalvular



# Important Considerations



1. Heterogeneity of control
2. *Post hoc* adverse event definitions
3. Neurological damage
4. Vascular injury
5. Aortic Insufficiency
6. **Patient selection**

# Patient Selection Issues

## Inclusion:

6. The subject, after formal consults by a cardiologist and two cardiovascular surgeons agree that medical factors **preclude operation**, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%.

## Exclusion:

19. Life expectancy < 12 months due to non-cardiac co-morbid conditions.

# Patient Selection Issues



- Qualitative judgement at individual sites – In-person assessment only at the center
- Enthusiasm for devices tests limits of patient selection – refined during trials
- Inclusion/Exclusion criteria did not address patients in long-term care facilities; no measure of return home vs rehab facility
- Need to consider when transcatheter valve implantation may not have a positive impact on a patient's quality of life
- The following 3 patients are not unique examples of patients with comorbidities – obtained from CEC narratives

## 87-year-old male

- non-ischemic cardiomyopathy, pacemaker, EF 20%, HTN
- Paget's disease, debilitating rheumatoid arthritis with multiple exacerbations and peripheral myopathy, post-herpetic neuralgia with severe chronic pain
- Randomized to SAPIEN, post-procedure complications (transient delirium, probable aspiration pneumonia, episodes of hypotension in the setting of volume overload/overdiuresis, laryngeal edema)
- discharged to a rehab facility POD #20, readmitted due to probable aspiration pneumonia, sepsis and death

## 95 YO male

- CAD (prior PCI, CABG), afib (warfarin), HTN, HL, renal insufficiency
  - COPD (home O2), macular degeneration (legally blind), history of CVA, subdural hematoma
  - SAPIEN implant, post-procedure stroke, reintubation, pneumonia, renal insufficiency, etc.;
- Transferred to acute rehab on POD#21, difficulty swallowing, pneumonia;
- Transferred home and died

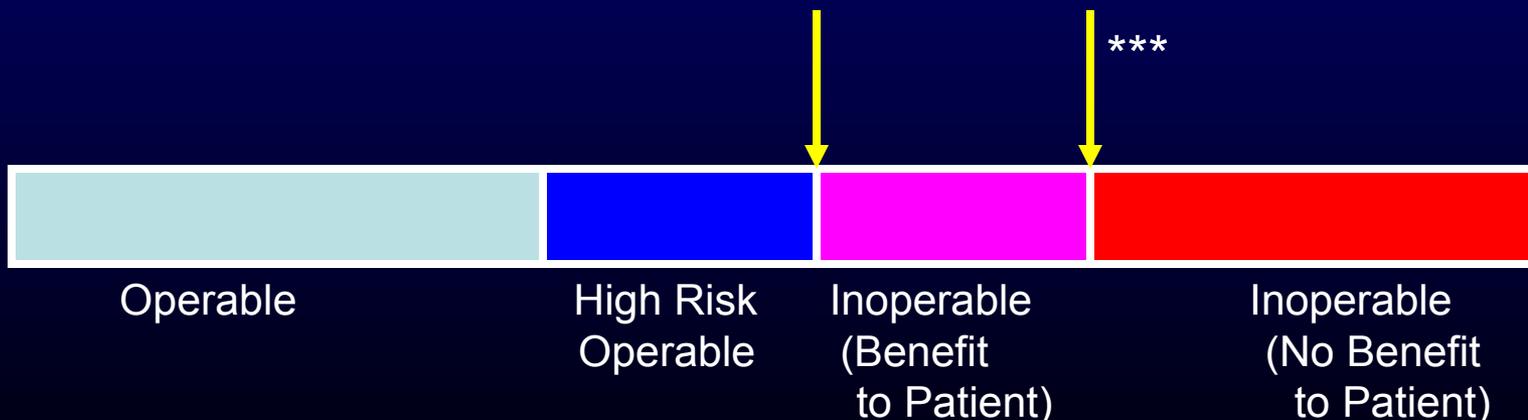
# 88 YO female

- CHF, CAD, afib (coumadin), HTN, severe Pulm HTN (72/32)
- Severe COPD with multiple admissions, home O<sub>2</sub>, FEV1 0.53; monoclonal gammaglobulinemia, osteoporosis, spinal stenosis
  - Left sided weakness (recurrent TIA's);
  - transferred from outside hosp. where she had transient left arm clumsiness (dx. TIA)
  - left arm became clumsy again - MRI = acute subacute stroke (MRA = decreased flow in right ICA, right MCA, b/l ACA, L PCA and stenosis R PCA, R proximal ICA)
- SAPIEN implanted, died 11 days later from progression of her stroke

# Patient Selection Issues

- No active consideration given to specifying patients who should not have transcatheter valve implantation due to extensive comorbidities
- SAPIEN implantation highly invasive (general anesthesia, 4+ hrs, contrast, TEE,  $\pm$  vascular operation)

Need to appropriately  
bracket use



# Summary of FDA Clinical Review



- The inoperable patients who received the SAPIEN device had an impressive **reduction in mortality** compared to those randomized to not receive the device
- This reduction in mortality in inoperable patients outweighed the **significant safety issues** with the device, most notably stroke and vascular injury
- Long term issues with the SAPIEN relating to clinically significant **aortic insufficiency and valve durability** remain to be defined
- **Patient selection** needs refinement
- Residential status needs to be considered in the endpoint

# **Post-Approval Study Considerations for SAPIEN Transcatheter Heart Valve**

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July 20, 2011

# Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating **a reasonable assurance of safety and effectiveness** and an appropriate risk/benefit balance

# Post-Approval Study Components

- Fundamental study question or hypothesis
- Well specified study population and study design
- Safety endpoints and methods of assessment
- Short term and long term safety and effectiveness endpoints and methods of assessment
- Duration of follow-up

# Important Postmarket Concerns for SAPIEN THV

- Long term device durability
- Long term patient quality of life
- Learning curve assessment
- Comparison of postmarket patients with premarket cohort, differences in patient populations and outcomes (including stroke), and device durability, and patient quality of life

# Proposed Post-Approval Studies

- Extended Follow-up of the Premarket Cohort
  - “PAS 1”
- New Enrollment Study
  - “PAS 2”

# Outline for Extended Follow-up of Premarket (PAS 1)

- Study Objectives
  - To assess: 1) long term (5-year) valve implant durability  
2) long term (5-year) quality of life
- Study Hypothesis
  - No hypotheses for: Durability or Quality of Life

# Outline for Extended Follow-up of Premarket (PAS 1), cont

- Population and Sample Size
  - Includes IDE participants who remain alive and return for clinical visits
  - Limited long term data with 10-30% of Sapien patients and “virtually no” comparator patients expected to be alive at the 5 year visit
- Follow-up through 5 years post implant
  - Evaluation of data at 4 years and 5 years post implant
- Endpoints
  - Durability measured by echocardiography at 4 and 5 years post implant
  - Quality of Life measured by SF-12 at 4 and 5 years post implant
  - Only observed data included in evaluation

# FDA Assessment – PAS 1

- Hypothesis and Power
  - Given long-term sample size, hypothesis and power calculation provide information regarding robustness of findings
- Outcomes
  - Collection of echo data included in current study
  - Modification of informed consent to collect quality of life data
  - Panel discussion requested

# Outline for New Enrollment Study (PAS 2)

- Study Objectives

To assess:

- 1) safety (including stroke)
- 2) adherence to indication and learning curve assessment (effectiveness)
- 3) long-term valve durability and quality of life in the post approval population

- Study Hypotheses

$$H_0 : D = P_T - P_C \geq \delta$$

$$H_1 : D = P_T - P_C < \delta$$

Where:  $P_T$  is event rate in registry,  $P_C$  is event rate comparison,  $\delta$  is non-inferiority margin (1.3 x performance goal)

# Outline for New Enrollment Study (PAS 2), cont

- Population and Sample Size
  - 750-1000 participants at a minimum of 75 sites
  - Study does not include sites with < 50 implants per year because not intended to be included in first year of commercialization
- Follow-up
  - 5 years post implant

# Primary Safety Composite Endpoint (PAS 2, 30-days post implant)

- All- cause mortality
- Major stroke
- Life-threatening (or disabling) bleeding
- Acute kidney injury - Stage 3
- Peri-procedural myocardial infarction
- Repeat procedure for valve-related dysfunction

# Primary Effectiveness Composite Endpoint (PAS 2, 1-year post implant)

- All-cause mortality
- Failure of current therapy for aortic stenosis, requiring hospitalization for symptoms of valve-related decompensation
- Prosthetic heart valve dysfunction

# FDA Assessment – PAS 2 Outcomes

- Composite endpoints:
  - could be heavily influenced by one component, such as death, or
  - this may not provide an accurate picture of the safety or effectiveness of the device for components of interest, such as major stroke
- Not all stroke specific hypothesis driven comparison proposed
  - only major stroke included in the composite primary safety analysis
  - all stroke is a secondary endpoint without specific hypothesis driven comparison

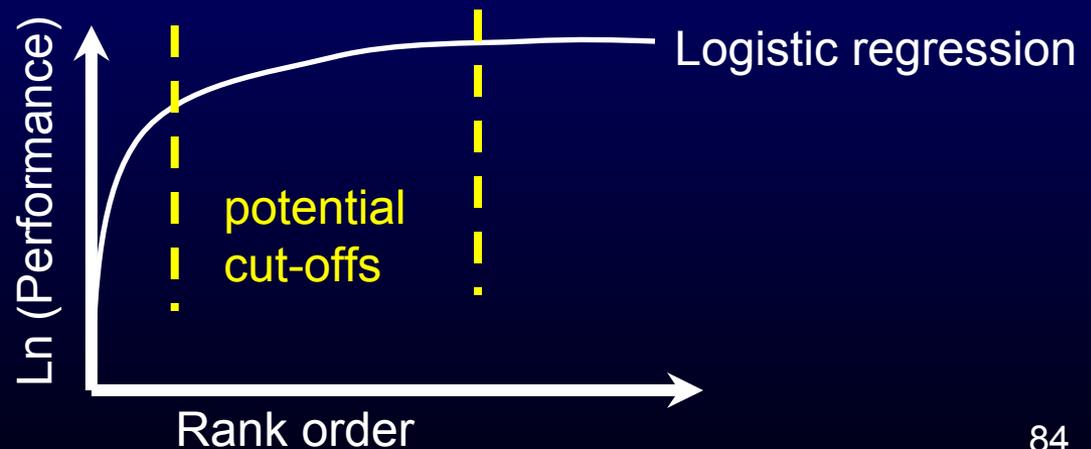
# FDA Assessment – Further Consideration for PAS 2

- Notable secondary endpoint
  - All neurological events (major and minor stroke and TIA – VARC) at 30 days and 1 year
- Vascular complications not characterized within the study
  - High proportion of major vascular complications were observed in the Sapien arm of the premarket study.
- Anticoagulation protocol based on stroke risk in patients with atrial fibrillation
  - Not validated in this population

# PAS 2 - Learning Curve

- Primary assessment via benchmarking of safety and effectiveness composite endpoints
- Secondary analyses of outcomes using analysis of patients ranked by order of implant in separate models by site and by interventionalist

$$\frac{\text{expected}}{\text{observed}} = \text{performance}$$



# FDA Assessment – PAS 2 Learning Curve Evaluation

- Max of 20 patients per site with less patients expected for each interventionalist learning the procedure
  - patients per interventionalist may be inadequate for ROC curve evaluation
  - may prevent comparison of outcomes associated with “earlier” and “later” patients treated by the same interventionalist
- Learning curve consists of (1) technical aspects of procedure *and* (2) appropriate patient selection.
  - no assessment of learning appropriate patient selection was proposed

# Panel Discussion

- Appropriateness of assessment of longer-term outcomes and quality of life, learning curve, and postmarket patient concerns
- Time frame, evaluation, and presentation of learning assessment to clinical community
- Use of VARC composite endpoints
- Use of performance goals derived from premarket data
- Recommended study questions and study design



# Summary of FDA Review

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# Summary of FDA Review



- Primary safety and effectiveness endpoint was met -  
The inoperable patients who received the SAPIEN device had an impressive reduction in mortality compared to those who did not receive the device
- A number of other factors should be considered in the evaluation of the overall risk-benefit profile of the device
  - These are the key areas where we are seeking panel input

# Request for Panel Input

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- Proposed indications for use
  - Does this language accurately describe the patient population where the risk-benefit profile is most favorable?
- Patient selection
  - How do you ensure that the appropriate patients get this device (inoperable patients who will benefit from correcting aortic stenosis)?
- Heterogeneity of the control group
  - How does this impact interpretation of the study results as well as labeling claims?

# Request for Panel Input



- Neurological adverse events
  - Based on the PARTNER trial and worldwide experience, this remains a concern for TAVI
  - What measures can be taken to mitigate this risk?
- Vascular complications
  - 1<sup>st</sup> generation device/delivery system
  - Does the training program adequately address ways to minimize this risk?
- Aortic Insufficiency
  - Aortic regurgitation is appreciable at 1-year
  - The long-term clinical significance is unknown

# Request for Panel Input



- Valve-in-valve technique
  - Widely used in worldwide experience
  - No preclinical testing and limited clinical data
  - How should this be addressed in the device labeling?
- Long-term valve durability remains unknown
- Need for post-approval study
  - Determine adverse event rate in “real world” use
  - Learning curve assessment
  - How do you interpret quality of life data in unblinded trials?
  - How long should these patients be followed?

**Questions?**