

# **A Critical Appraisal of Percutaneous Aortic Valve Therapies: Device Concepts, Clinical Outcomes, and Future Projections**

***Martin B. Leon, MD***

***Columbia University Medical Center  
Cardiovascular Research Foundation  
New York City***

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## Presenter Disclosure Information for Angioplasty Summit 2007

***Martin B. Leon, M.D.***

***Consultant or Advisory Board:***

Sadra, Edwards Lifesciences

***Stockholder or other Equity:***

Sadra



# The FIRST Human Heart Transplant

*A crowded operating room!*



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# What about a human heart valve transplant?



**Transcatheter AVR at Columbia!**



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# Transcatheter AVR

## Indications for Surgical AVR

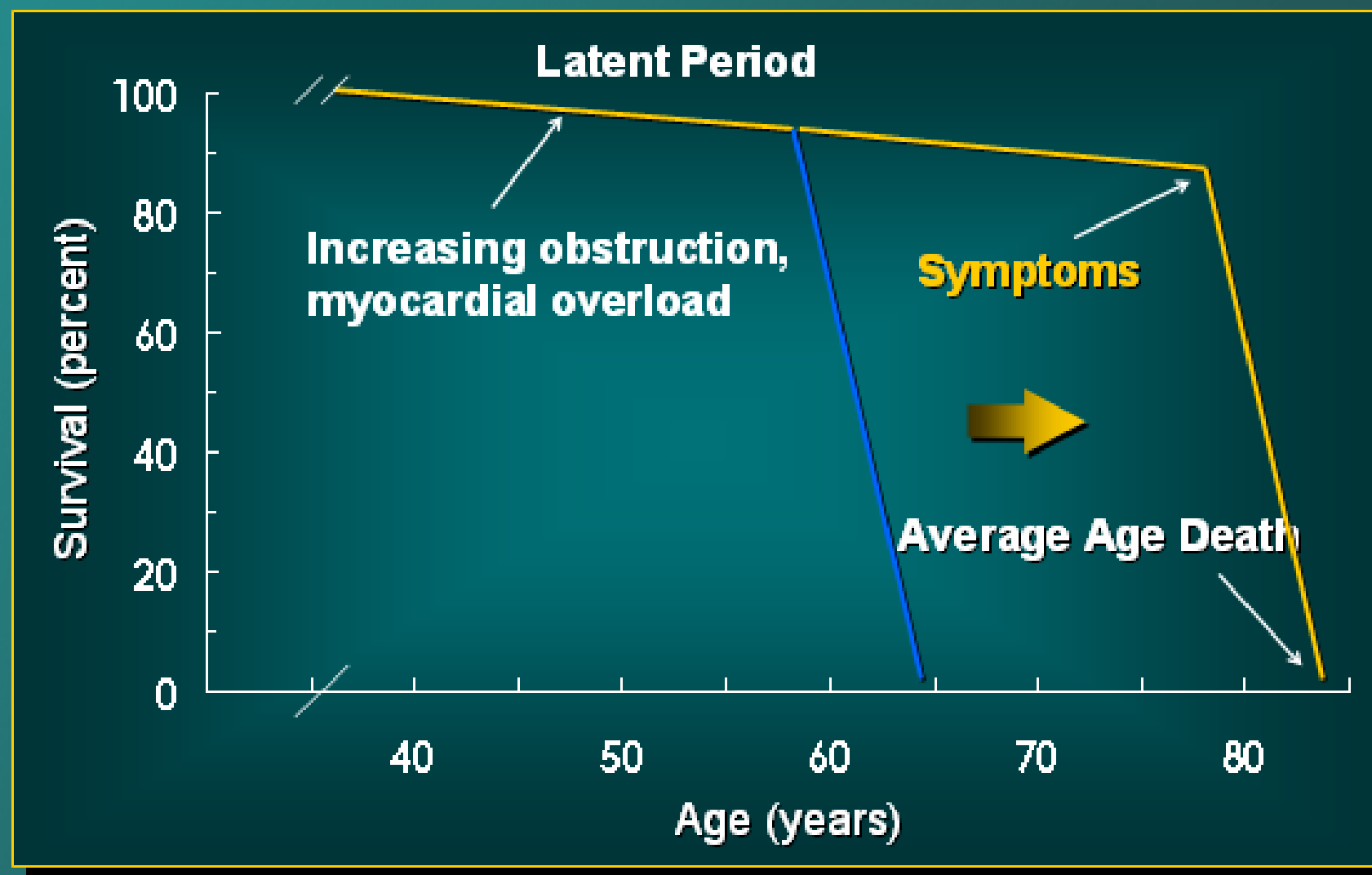
***Why is surgical AVR so great?***

Because our patients...

1. Live longer
2. Feel better (marked Sx benefit)
3. Have improved LV function



# Natural History of Aortic Stenosis



*from Ross and Braunwald, Circulation 1968*



# The Potential Population of AS Pts Requiring Treatment

	2004 Population	AS Prevalence	Severe AS	Severe AS 50% with Sx
<b>18-44</b>	125,841,694	0.10%	41,947	20,974
<b>45-54</b>	41,618,805	0.20%	27,746	13,873
<b>55-64</b>	29,078,924	0.60%	58,158	29,079
<b>65-74</b>	18,463,472	1.40%	86,163	43,081
<b>&gt;75</b>	17,830,513	4.60%	273,401	136,701
<b>Total</b>	232,833,408	—	<b>487,415</b>	<b>243,708</b>

Based upon the Olmsted County AS prevalence data and US population statistics, *the potential AS treatment cohort could exceed 250,000 patients!*

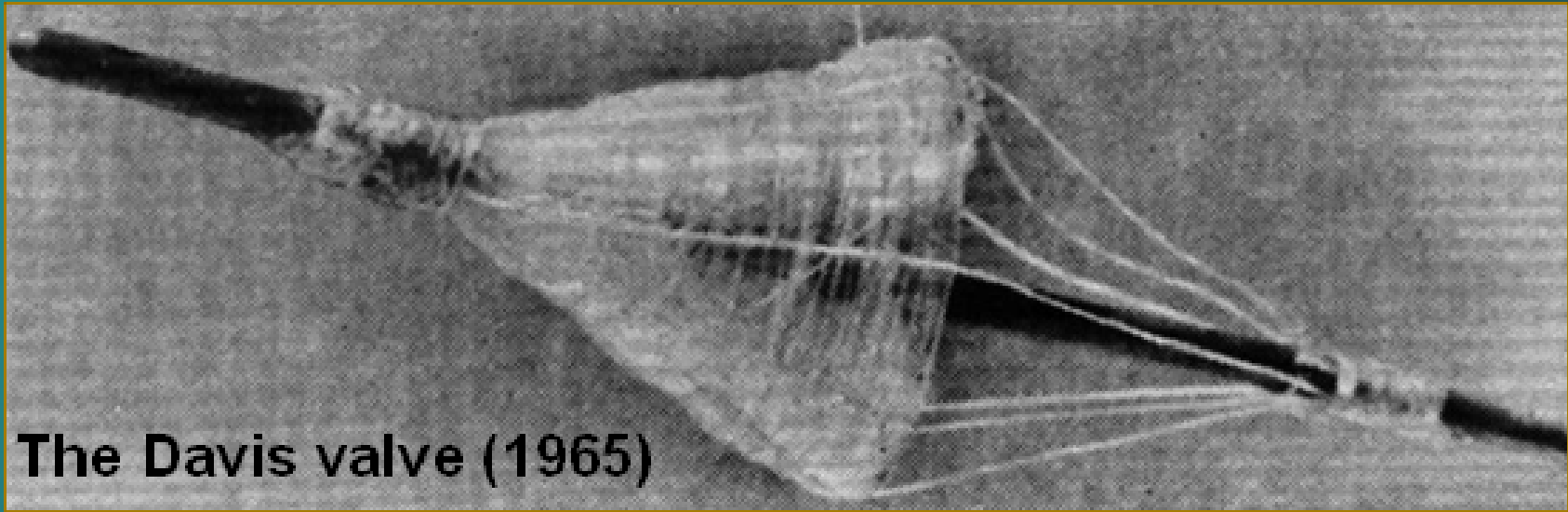


# Transcatheter AVR

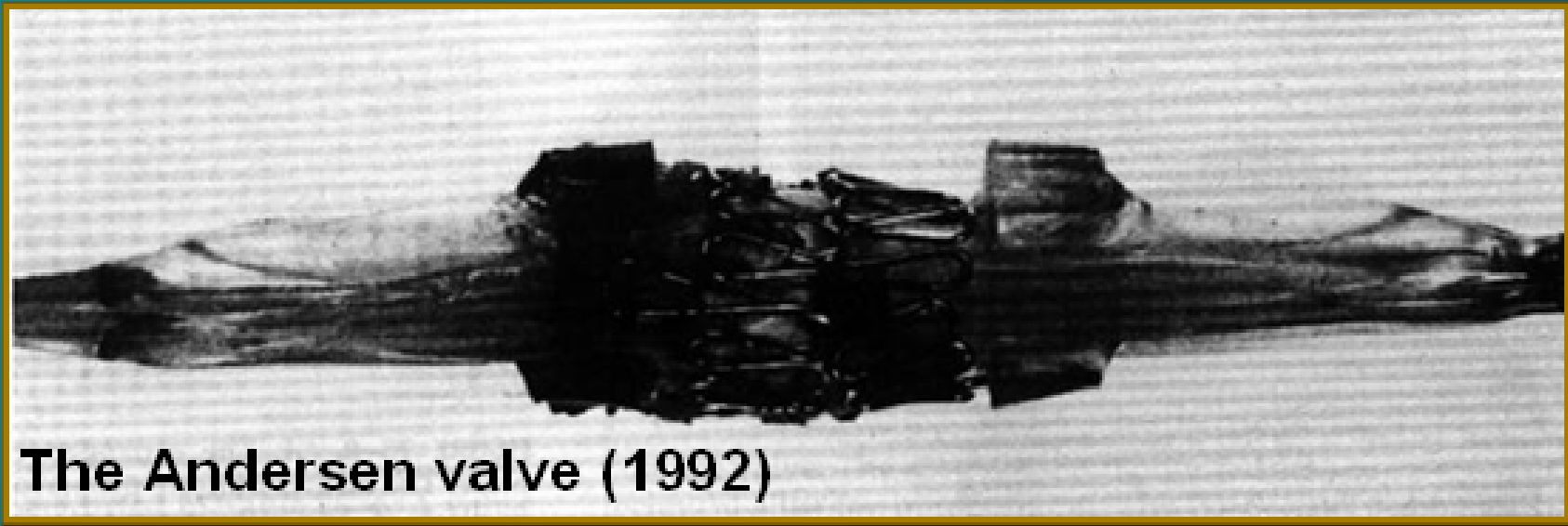
## Technology Overview...



# Early Catheter-Based AV Designs



**The Davis valve (1965)**



**The Andersen valve (1992)**



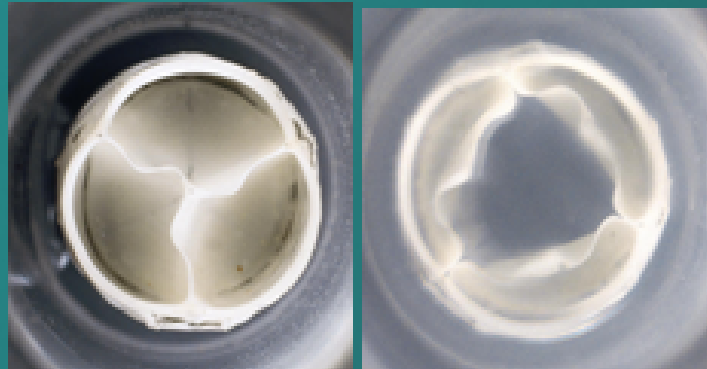
# Transcatheter AVR Systems

## *1<sup>st</sup> Generation*

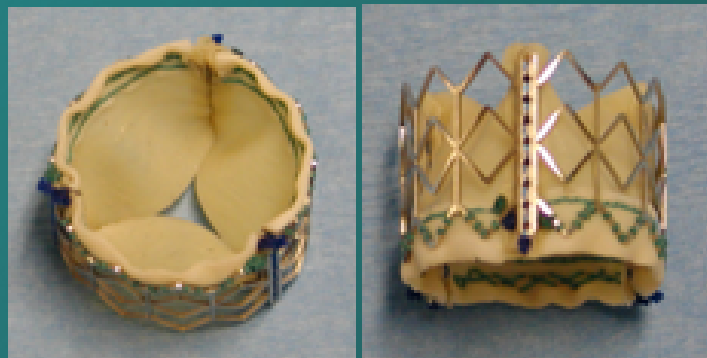
- **Cribier-Edwards Aortic Bioprosthesis**
  - Balloon expandable stainless steel bioprosthesis
  - Equine pericardial valve
  - Unsheathed and sheathed (FlexCath)
  - Antegrade, retrograde, or trans-apical approach
- **CoreValve Revalving™ System**
  - Self-expanding nitinol cage bioprosthesis
  - Porcine pericardial valve
  - Sheathed (21 Fr and 18 Fr)
  - Retrograde approach



# Cribier-Edwards Percutaneous Heart Valve



First generation – polyurethane



Second generation – bovine pericardium

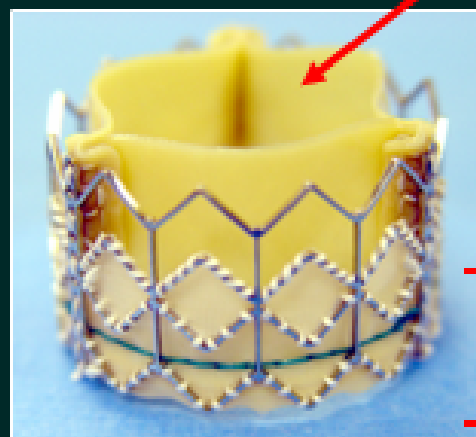
## Current Device



- equine pericardial valve
- stainless steel stent
- 23mm and 26mm diameters
- balloon-expandable
- AVA = 1.7-1.9 cm<sup>2</sup>



# The Next Generation: Edwards – SAPIEN THV

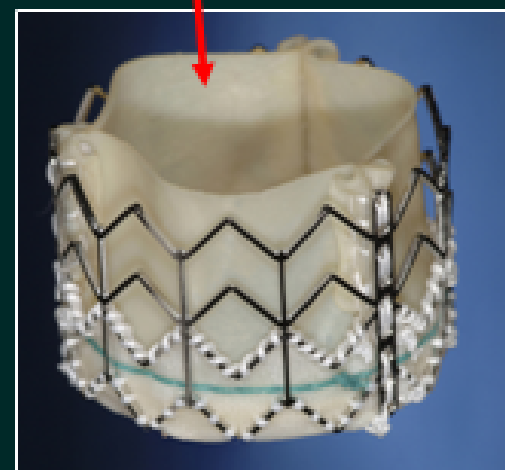


**Edwards-SAPIEN THV**

**Bovine Tissue  
ThermaFix Treatment  
Pericardial Mapping  
Leaflet Deflection  
Proprietary Processing**

**New  
Skirt Height**

**Untreated Equine  
Tissue**



**Cribier-Edwards PHV**

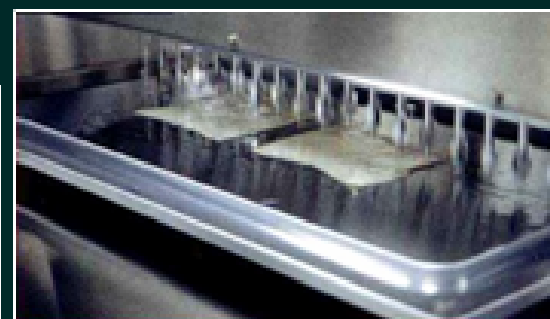
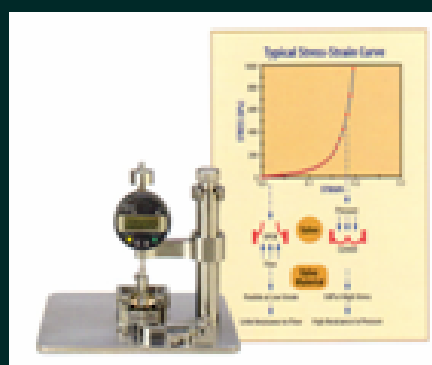
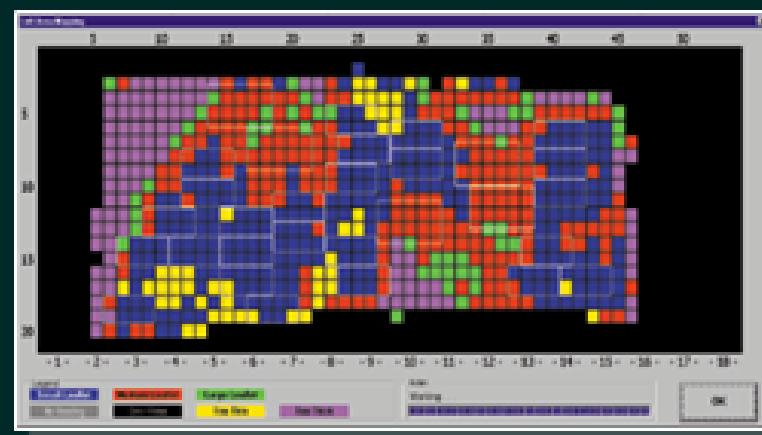
**Current  
Skirt Height**



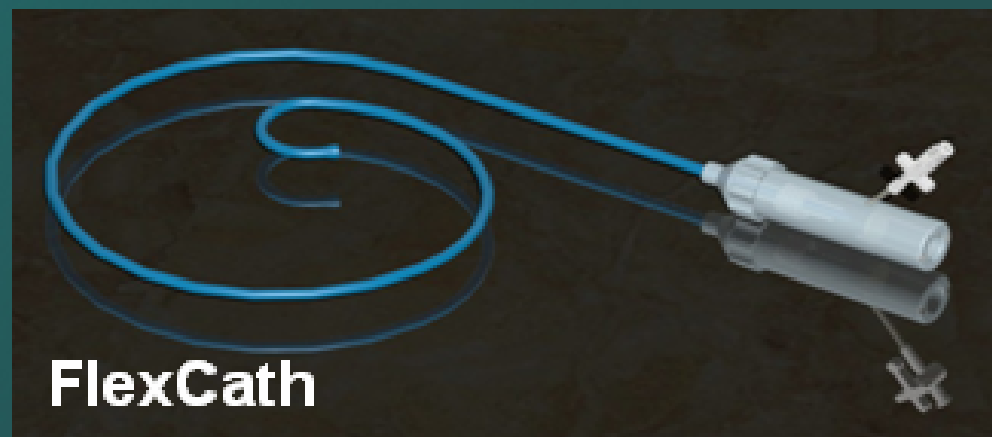
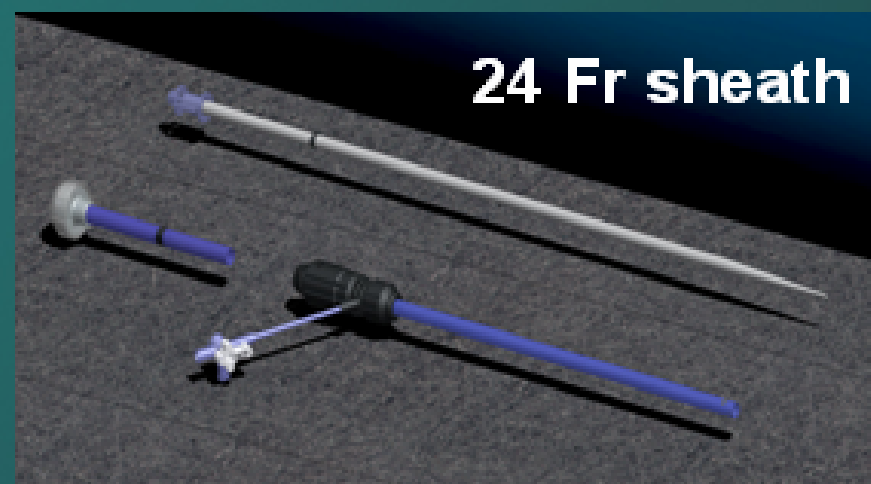


# Next Generation Valve Should Provide Surgical Valve Durability

- **PeriMap Technology**
  - Leaflets are optimally matched by thickness
- **Deflection Test**
  - Leaflets are matched for elasticity = improved coaptation and performance



# Cribier-Edwards Percutaneous Heart Valve **SYSTEM**

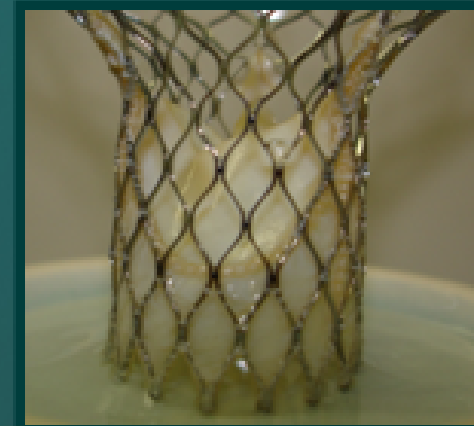


# CoreValve ReValving™ System

## 4 Components



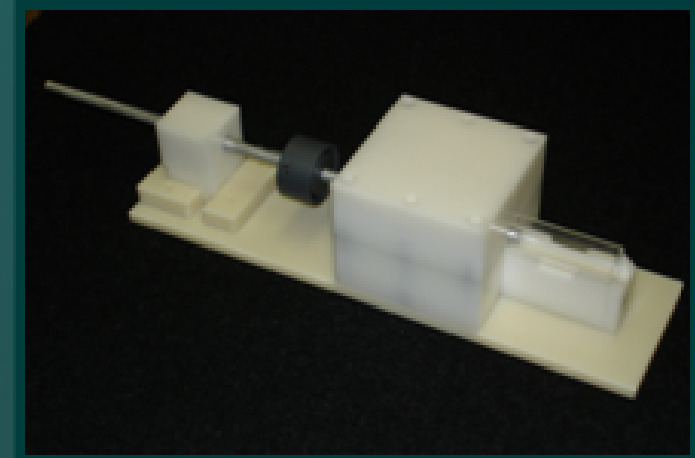
**1. Self-expanding multi-level self-expanding nitinol frame**



**2. Porcine pericardial valve**



**3. Sheathed delivery catheter;  
21 F (now 18 F)**

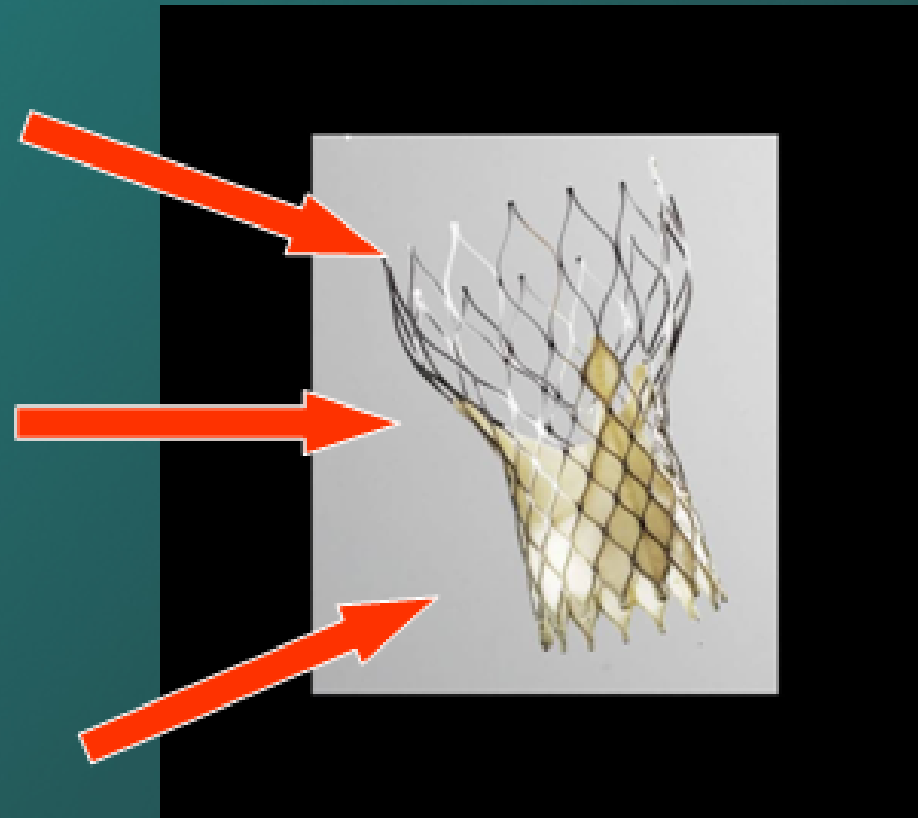


**4. Loading system**



# CoreValve Self-Expanding Bioprosthesis

- **HIGHER PART:** low radial force area axes the system and increases quality of anchoring
- **MIDDLE PART:** functional valve area with three leaflets and constrained to avoid coronaries (convexo-concave) – avoids need for rotational positioning
- **LOWER PART:** high radial force of the frame pushes aside the native calcified leaflets for secure anchoring and avoids recoil and para-valvular leaks



A porcine pericardial tissue valve  
fixed to the frame with PTFE sutures



# Transcatheter AVR

## Early Clinical Results...



# First successful percutaneous aortic valve replacement!



Day 8 post-implantation



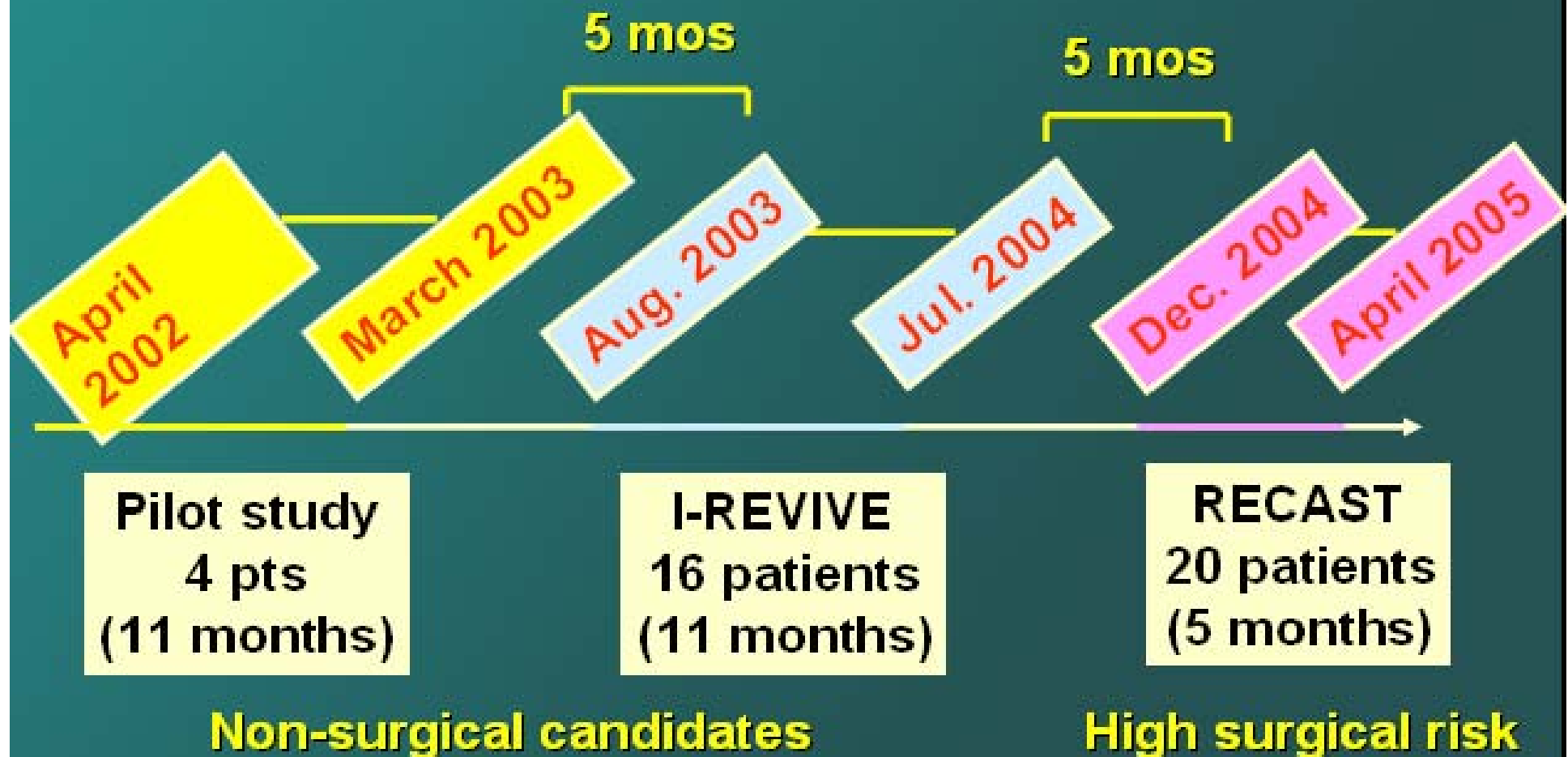
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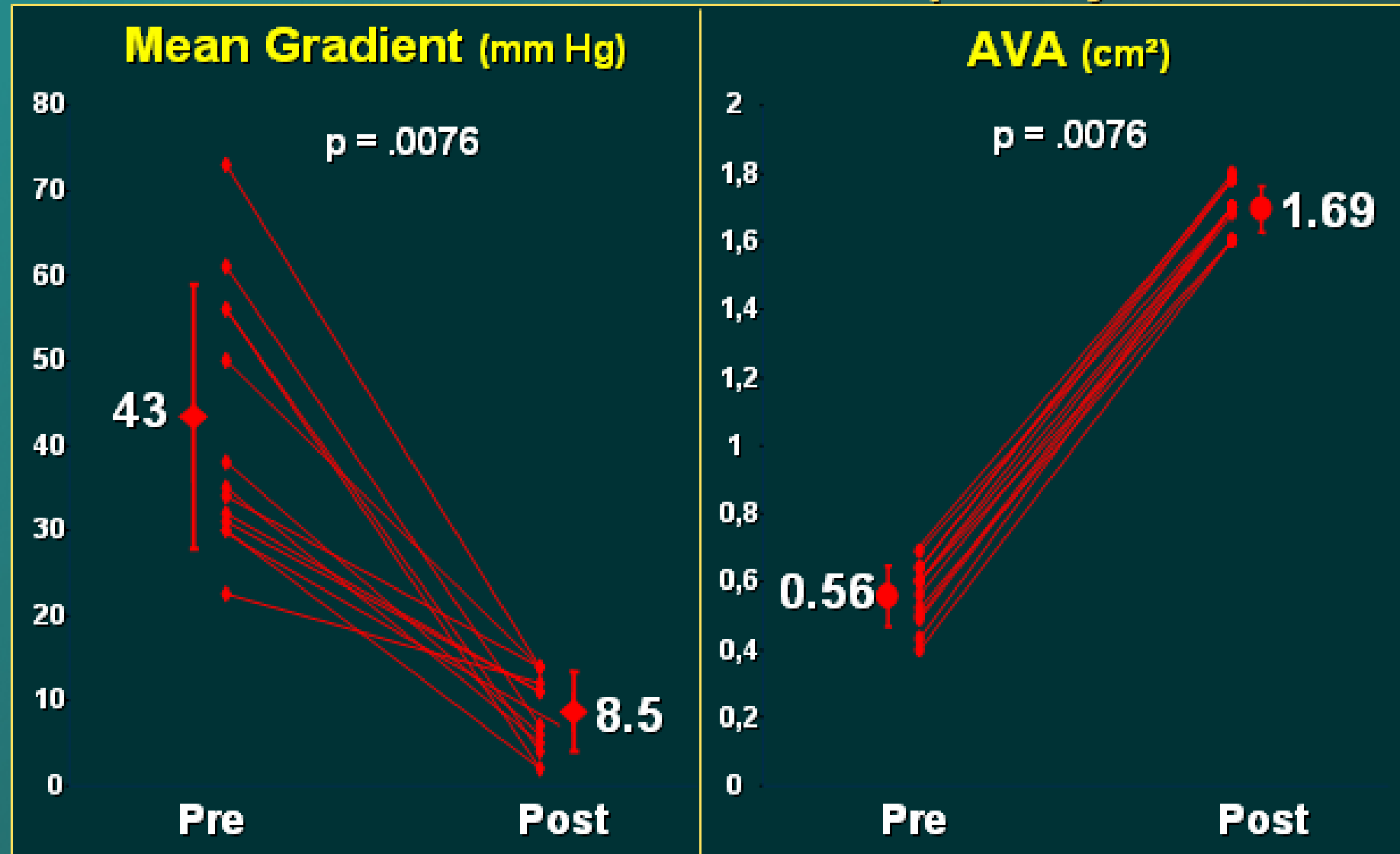
# Cribier – Early PHV Experiences

## *Rouen, France*



# Cribier – Early PHV Experiences

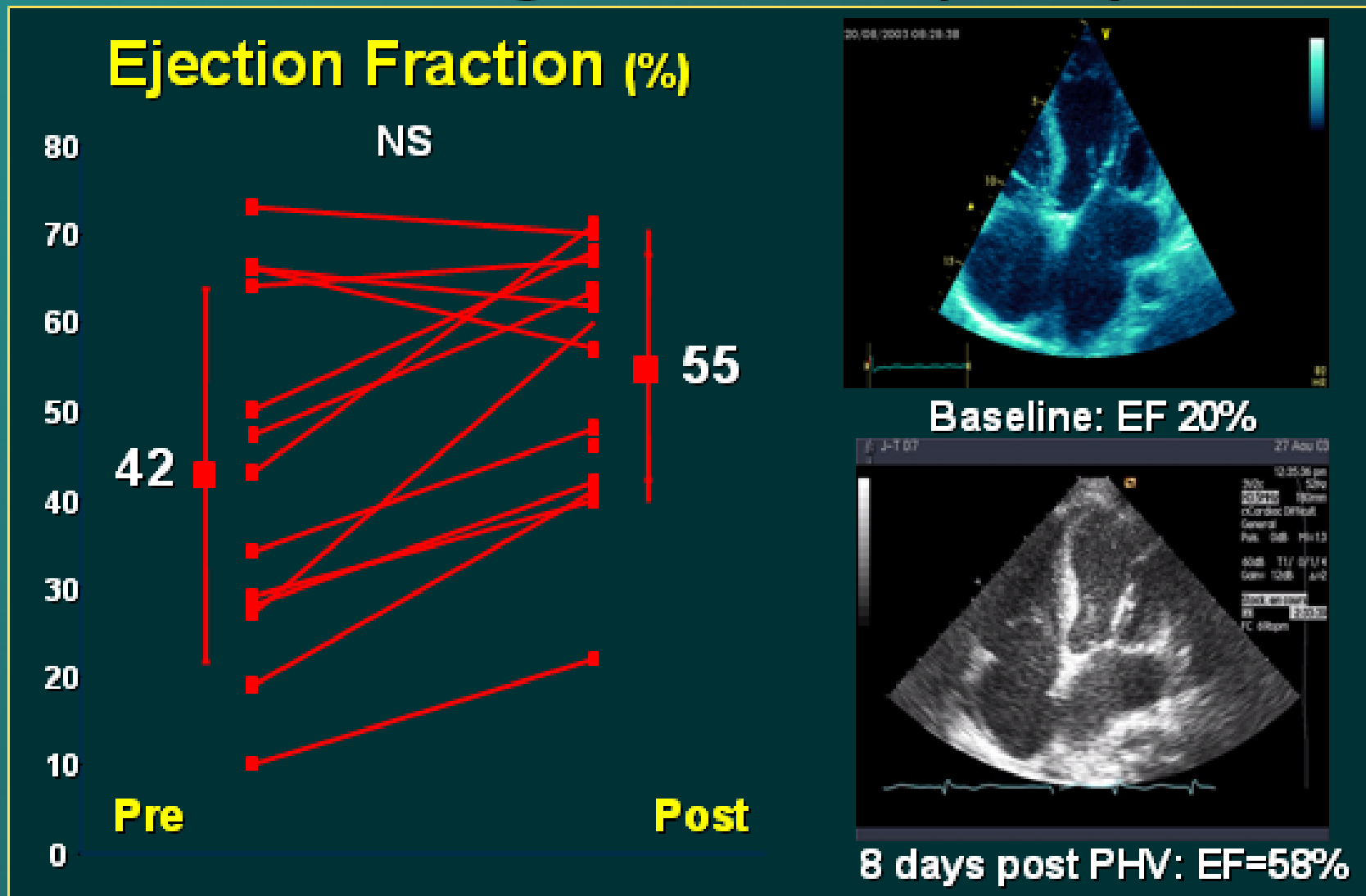
## *Procedural Results (n=16)*



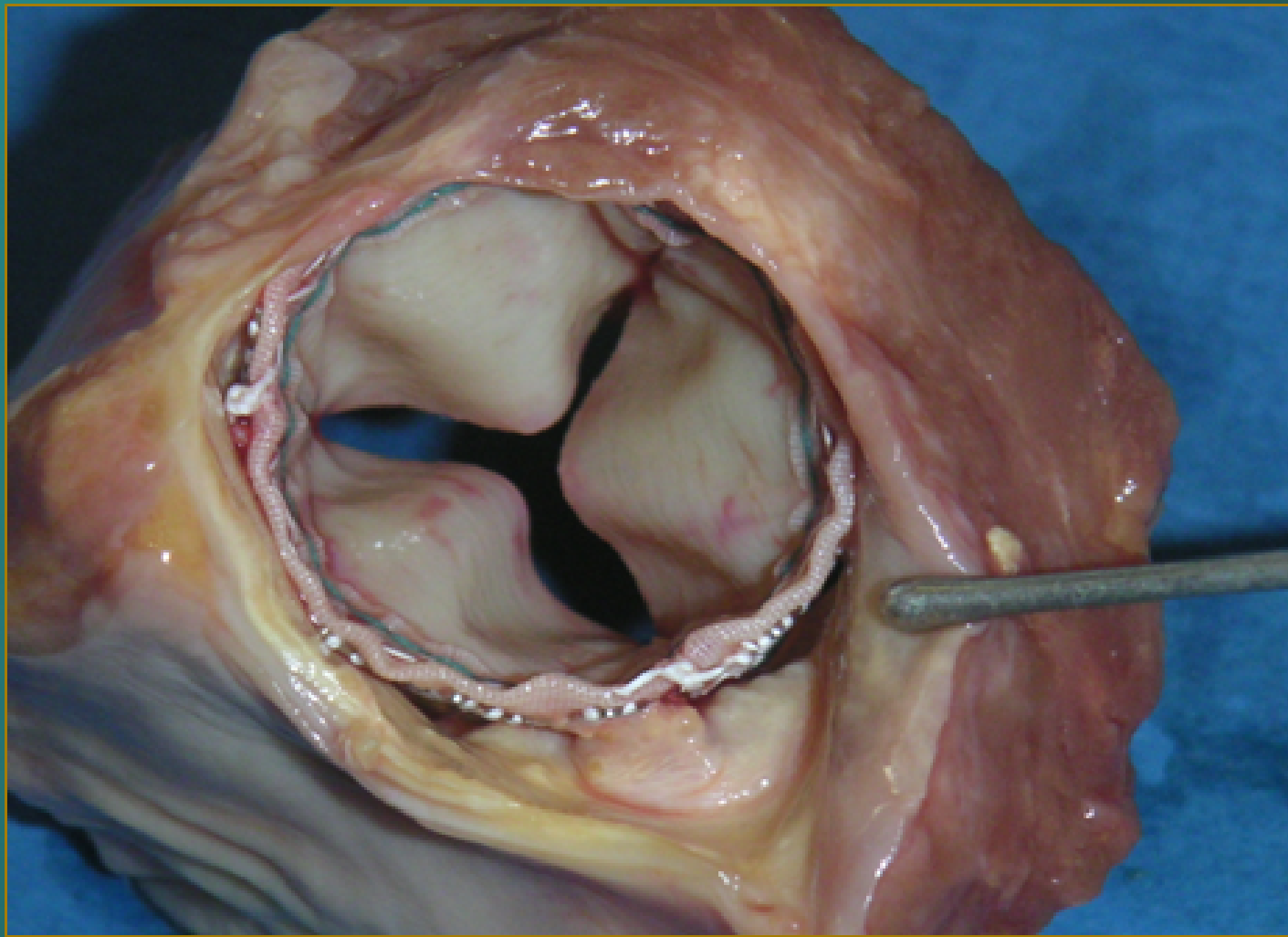


# Cribier – Early PHV Experiences

## *Changes in LVEF (n=13)*



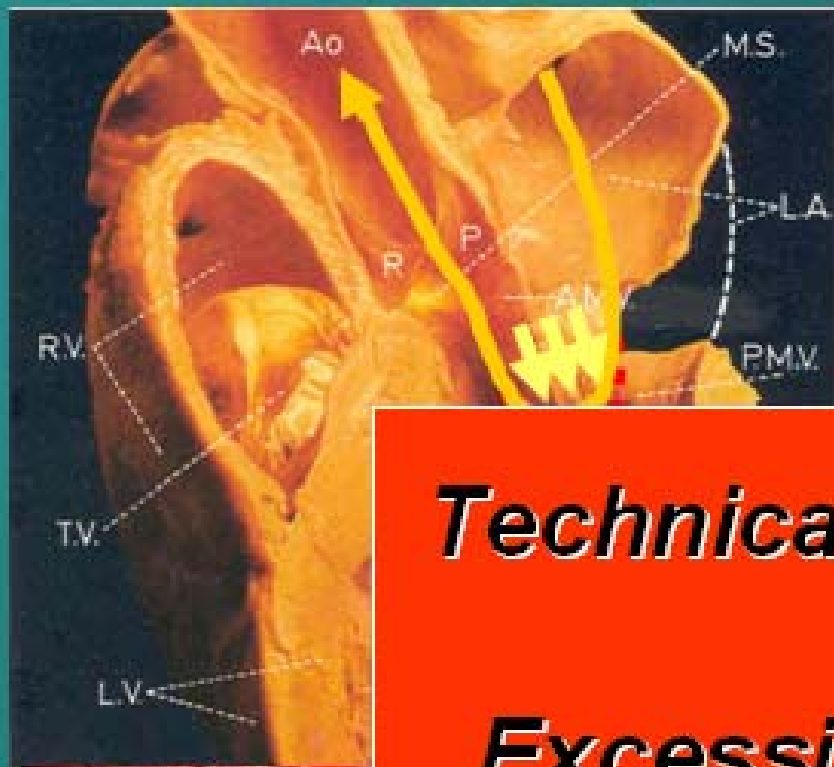
# Para-valvular Regurgitation



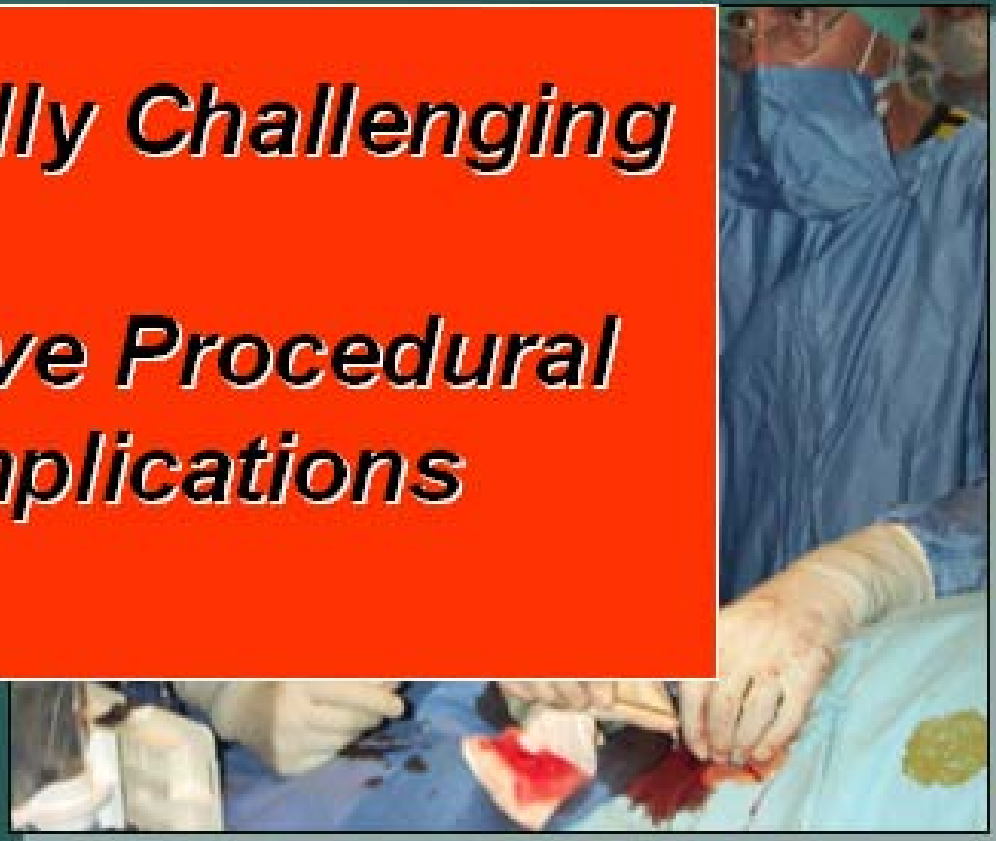
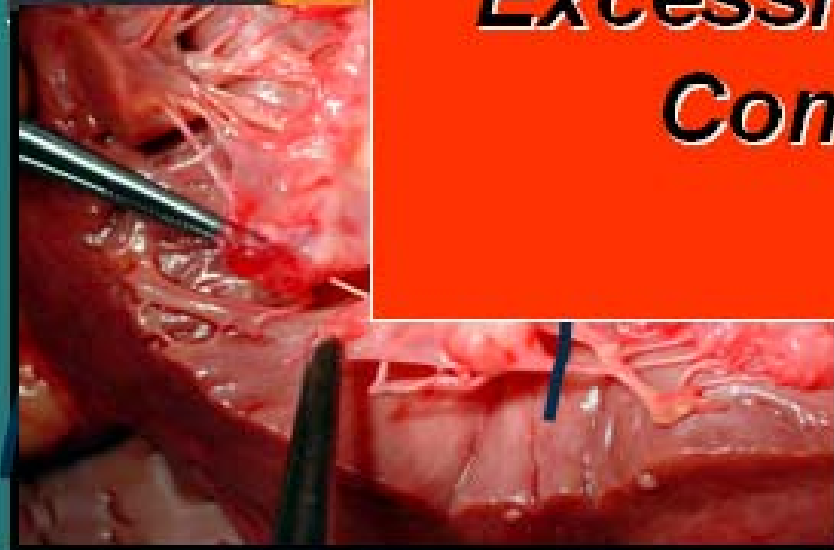
**Patient #5**



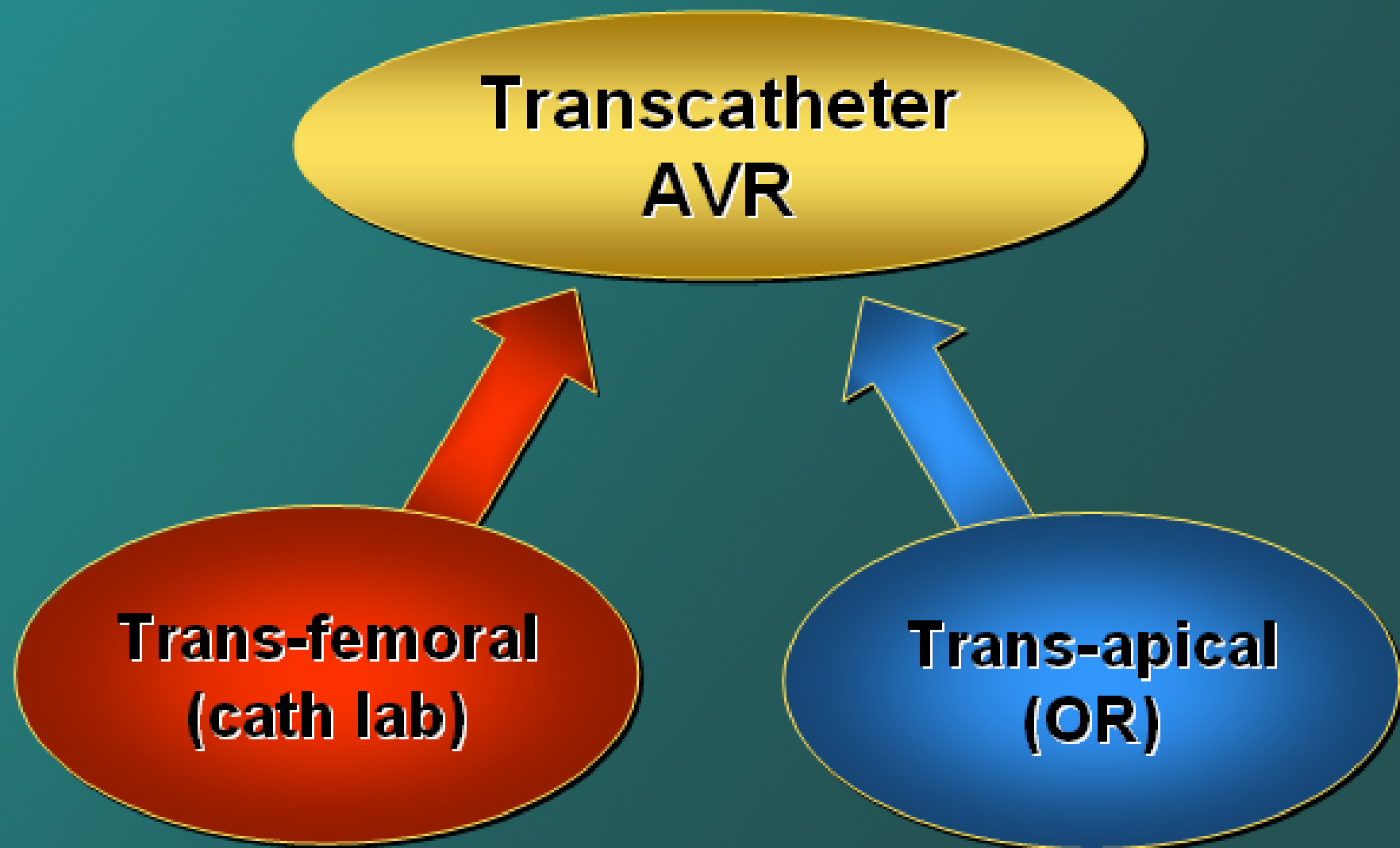
# Antegrade Approach: Guidewire Position in LV



***Technically Challenging***  
***Excessive Procedural***  
***Complications***



# Transcatheter AVR Technologies



# Transcatheter AVR Technologies

**Transcatheter  
AVR**

**Trans-femoral  
(cath lab)**

- Antegrade = femoral vein
- Retrograde = femoral artery



# Transcatheter AVR Technologies

**Catheter-Based  
AVR**

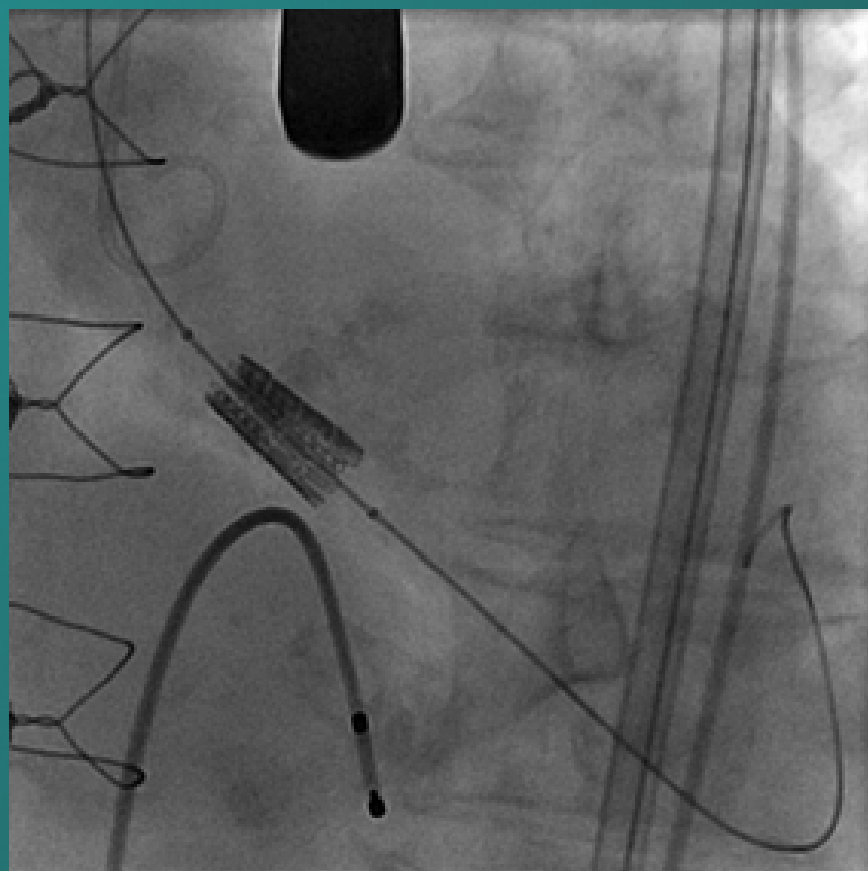
***Preferred***

**Trans-femoral  
(cath lab)**

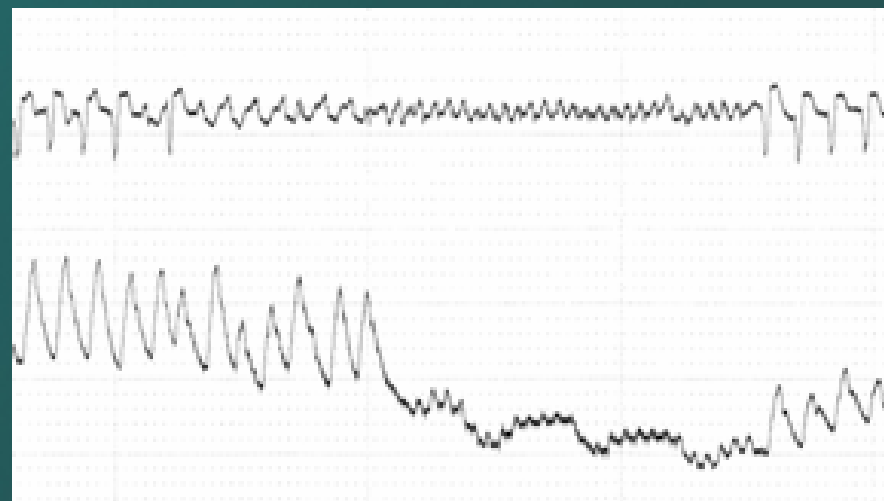
- Good vascular access
- No Ao arch pathology
- Retrograde AV crossing predictable



# Retrograde Trans-femoral Deployment



*Rapid pacing : 220/min*



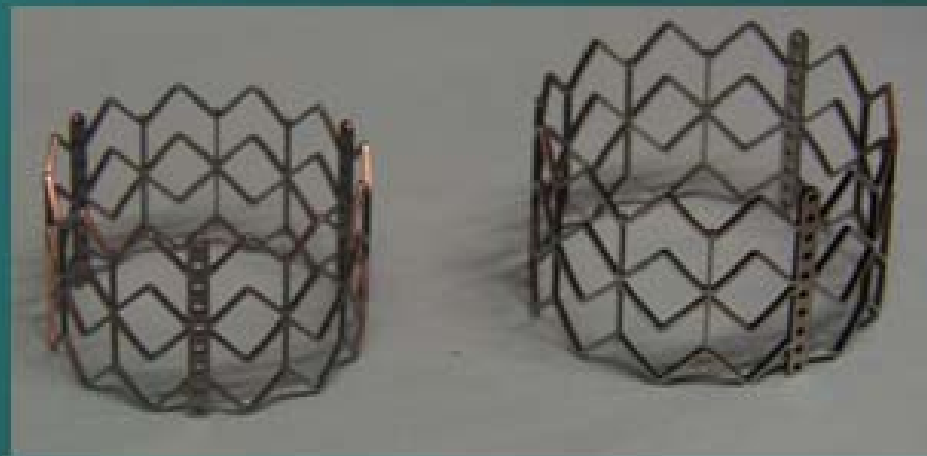
# The new 26 mm PHV



**23mm**



**26 mm**



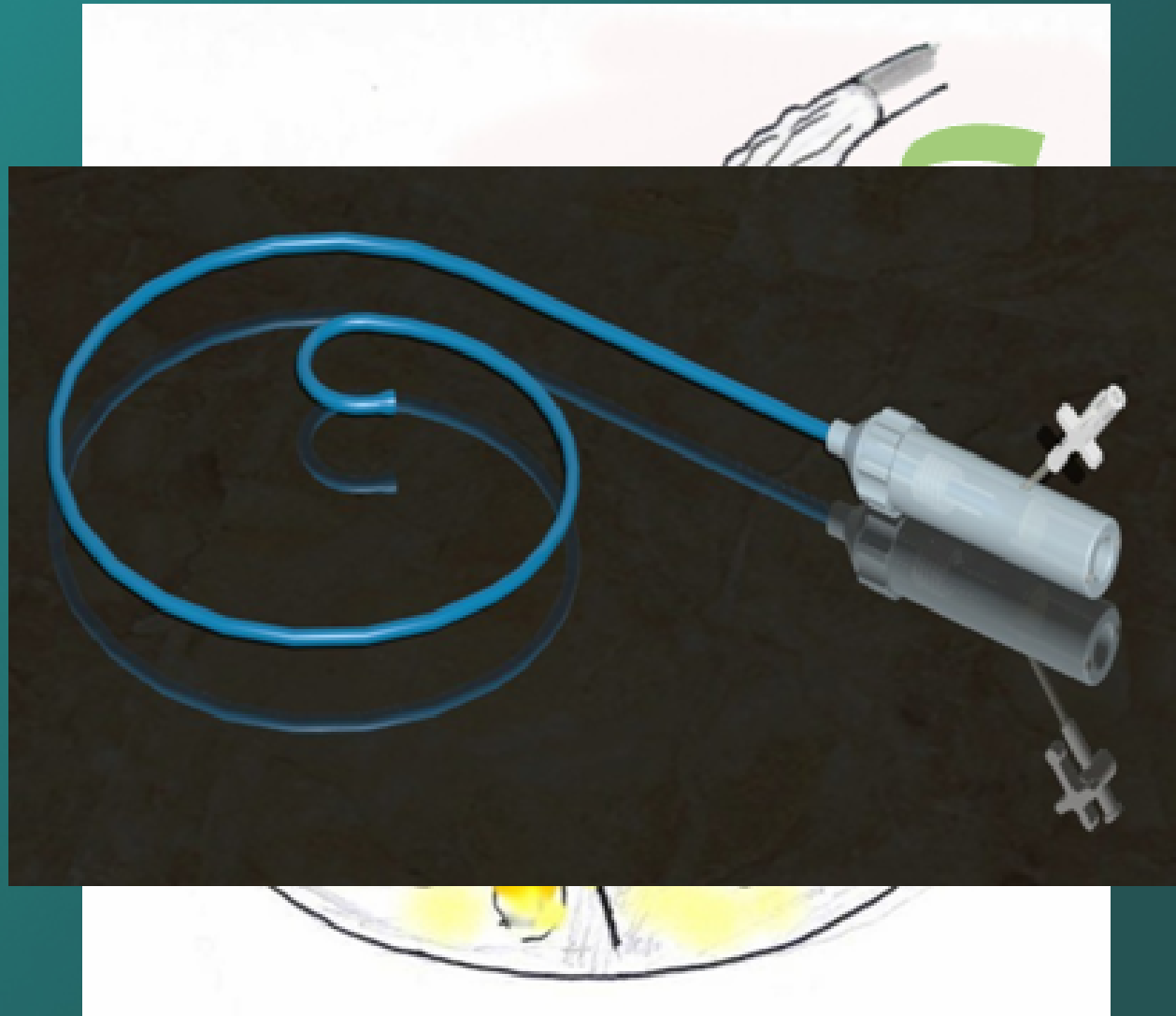
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# Edwards *Flex Cath* Delivery System

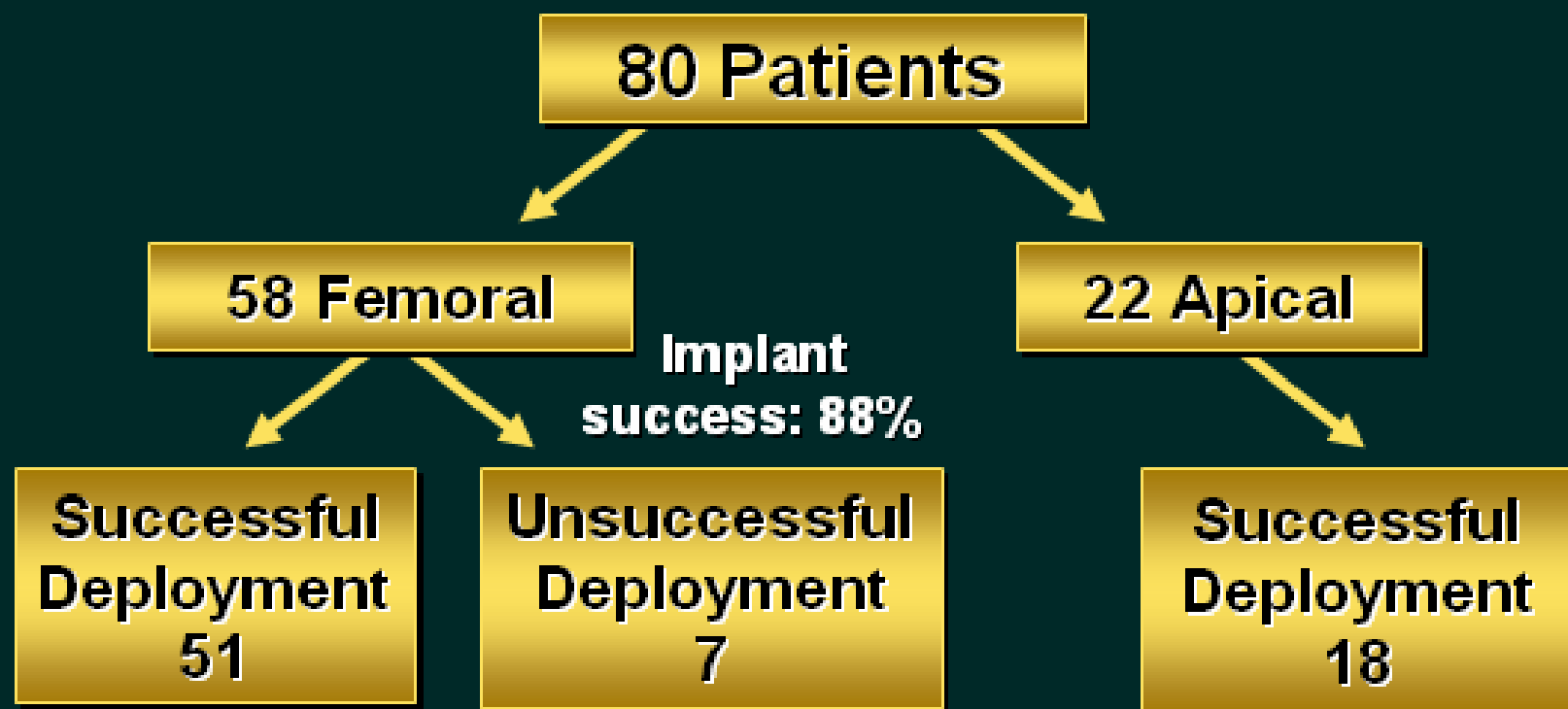


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# St. Paul's Hospital Vancouver Experience



30-day mortality: 12.1%

30-day stroke: 3.4%

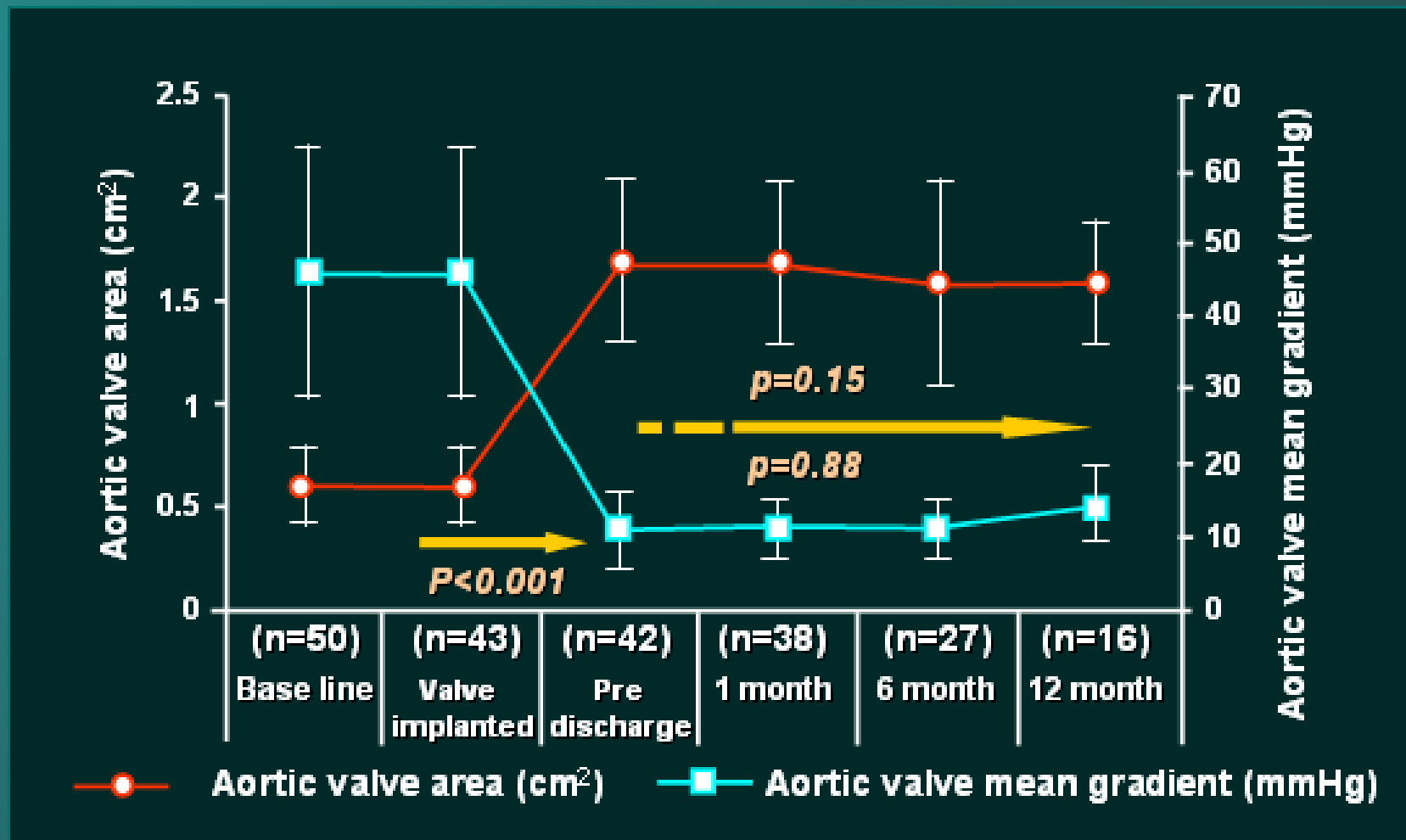
Logistic EuroSCORE: 28%

J. Webb and colleagues



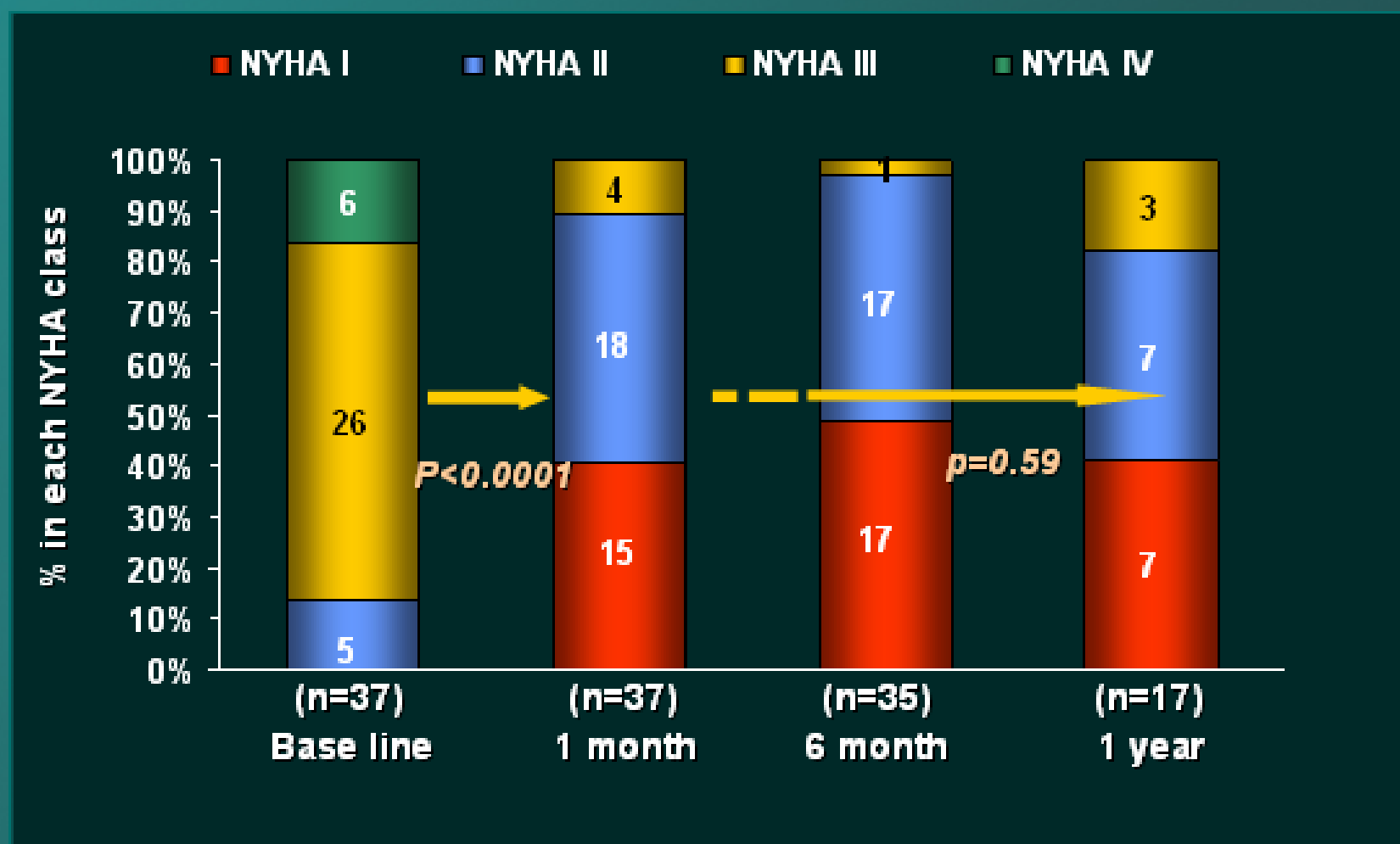
# tAVR: Vancouver Experiences

## AV Area and Gradients



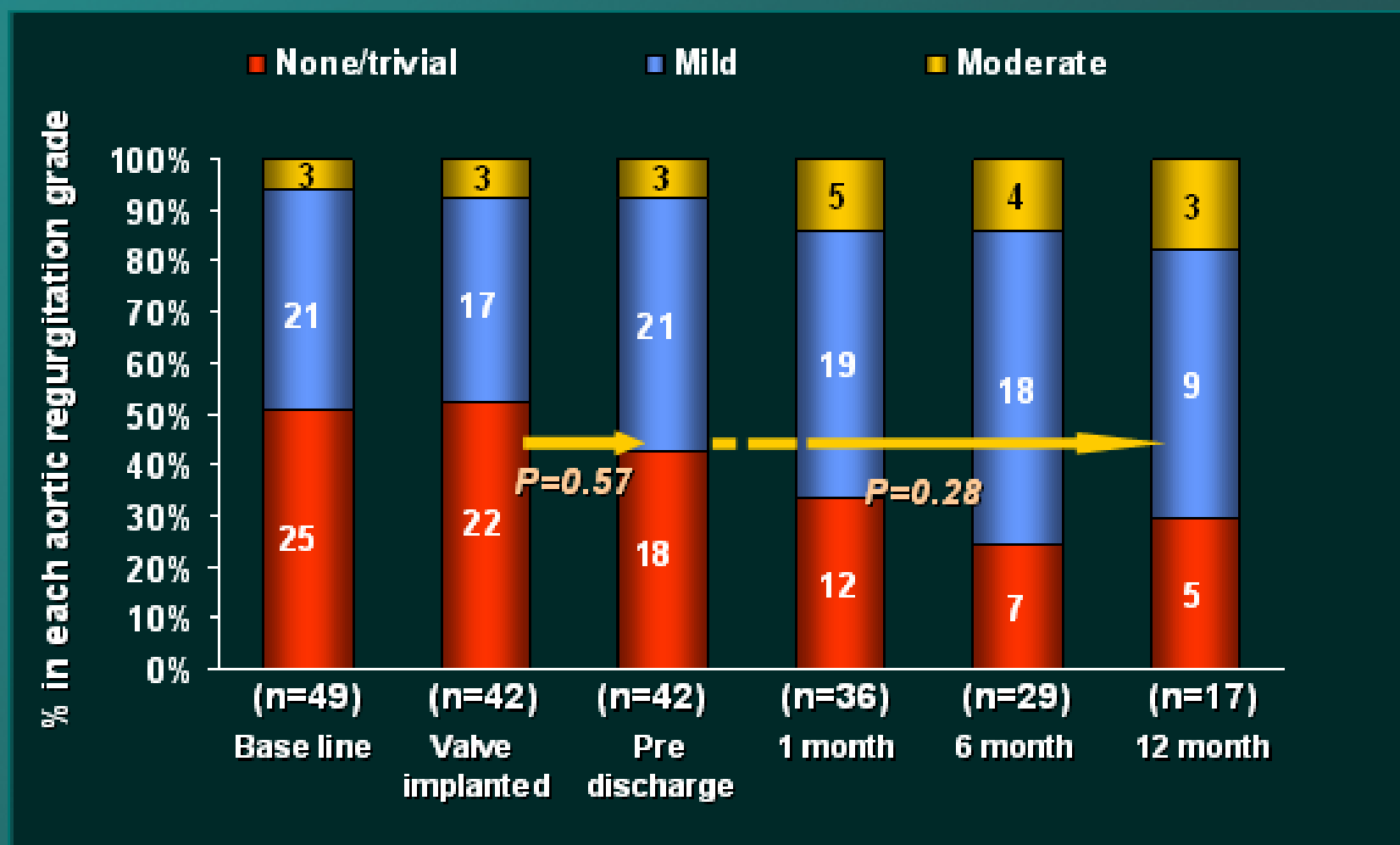
# tAVR: Vancouver Experiences

## Symptom Status



# tAVR: Vancouver Experiences

## *Aortic Regurgitation*



# Six Month Results from the PeRcutaneous EndoVascular Implantation of VALves Trial in High Risk Patients with Critical Aortic Stenosis

*Susheel K. Kodali, William O'Neill,  
Jeffrey W. Moses, Samir Kapadia,  
Mathew Williams, George Hanzel,  
Allan Stewart, Murat Tuzcu, Michael Collins,  
and Martin B. Leon*



# US Retrograde Cribier-Edwards Experience

## **REVIVAL II**

**55 Patients\***

**Trans-femoral  
55**

**Successful  
Deployment  
48**

**Unsuccessful  
Deployment  
7**

**30-day Mortality: 7.3% (4)  
30-day MACCE: 18.2% (10)  
Logistic EuroSCORE: 33%  
STS score: 13%**

### **Centers:**

29 Columbia  
15 Beaumont  
11 Cleveland  
Clinic

**PI: Wm O'Neill**

**Implant  
success: 87%**

**Failed access 3**

**Malpositioned valve 1**

**Unable to cross 3**



## Mean AV Gradients (n=42 pts)





# REVIVAL II – Clinical Outcomes

	In-Hospital	< 30 Day	6 Months *
<b>MACCE</b>	10 (18.2%)	10 (18.2%)	18 (30.9%)
Death	4 (7.4%)	4 (7.4%)	9 (16.4%)
MI	1 (1.8%)	1 (1.8%)	1 (1.8%)
Neurologic events	5 (9.0%)	5 (9.0%)	7 (12.7%)
Reop for valve failure	0	0	0
<b>Other</b>			
Vascular complication	7 (12.7%)	7 (12.7%)	7 (12.7%)
Repeat balloon dilatation	0	1 (1.8%)	2 (3.6%)
Device migration (post-proc)	0	0	0
Renal failure (req dialysis)	3 (5.5%)**	3 (5.5%)**	3 (5.5%)**

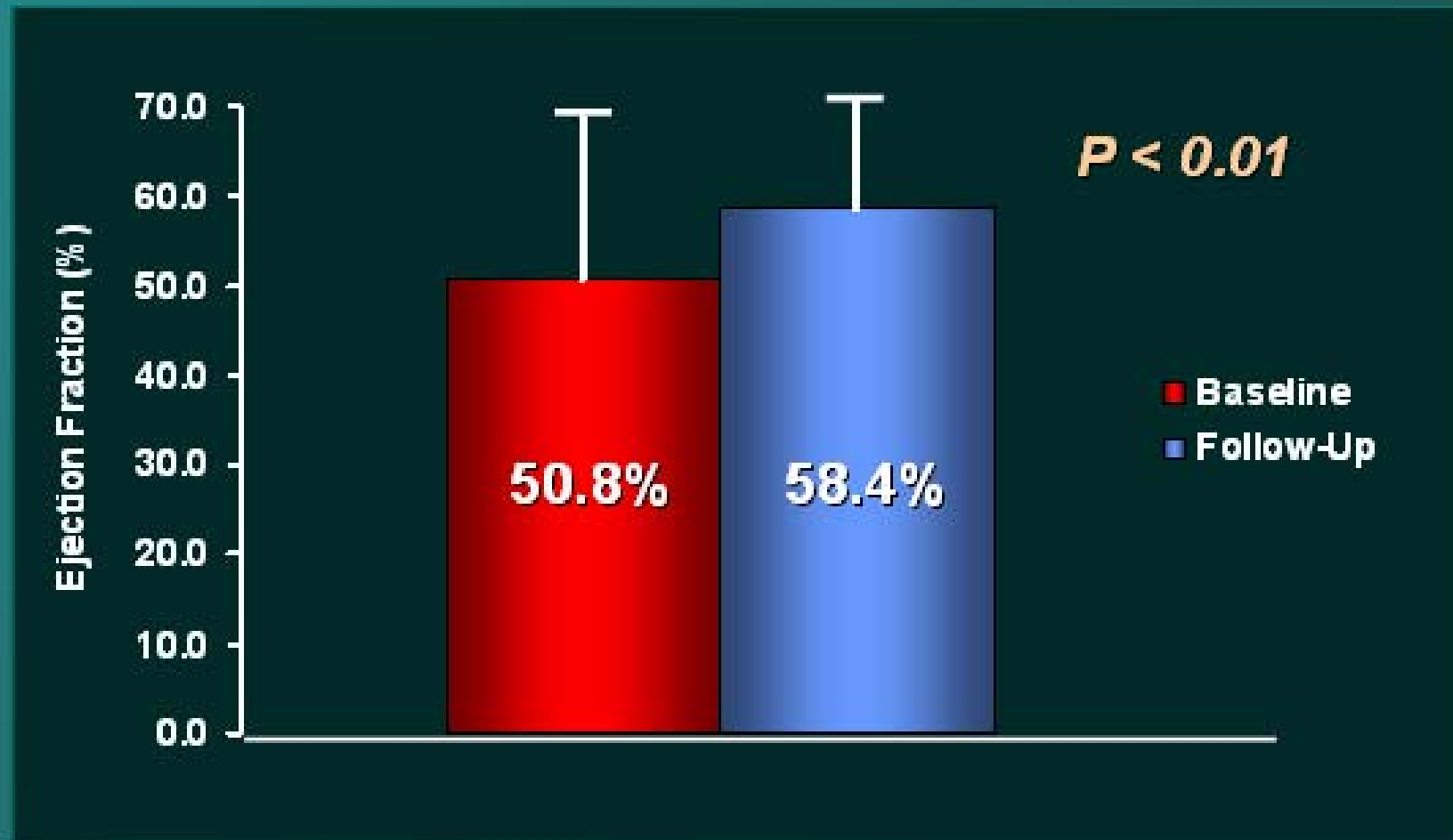
\* Two patients have not reached six month time point yet

\*\* One patient on CVVHD prior to valve implantation



## REVIVAL II

# LVEF Following Valve Implantation



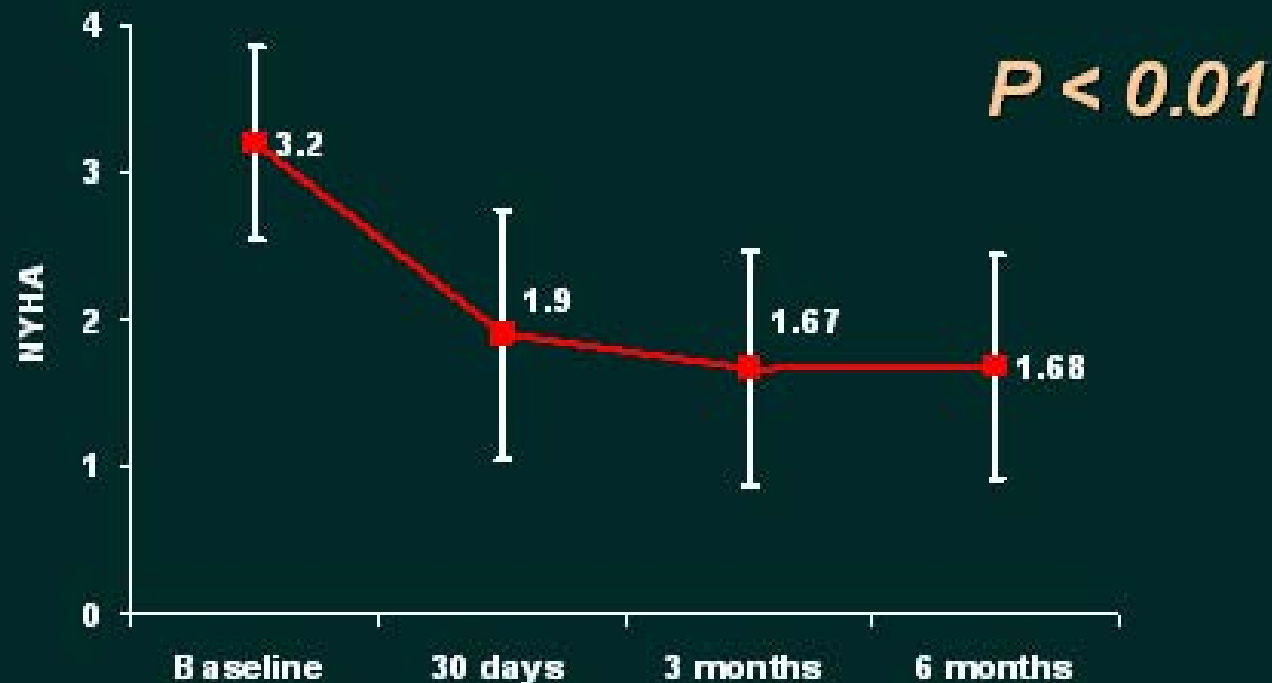
# REVIVAL II

## Aortic Valve Gradients



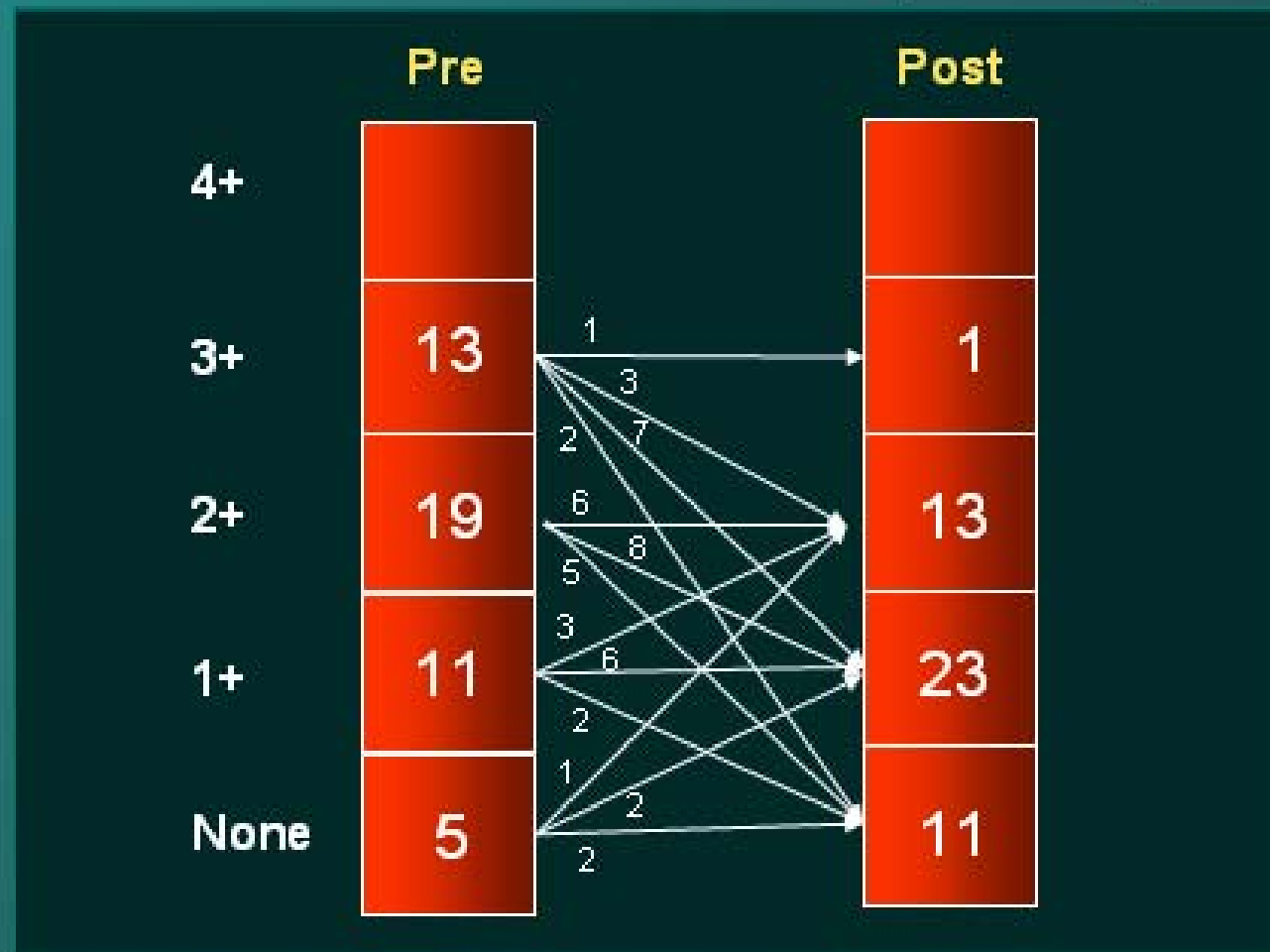
# REVIVAL II

## NYHA Class (to 6 months)



# *REVIVAL II*

## Aortic Regurgitation Post Procedure (n=48)



# Transcatheter AVR

## Case Example: CUMC (Aug 2006)

**POD #1**



**POD #3**



- 100 yo Holocaust survivor
- critical AS (AVA 0.2 cm<sup>2</sup>), CAD s/p CABG, PAH, CRI, and class IV CHF; EuSc (log) 49%, STS 29%
- 23mm Cribier-Edwards PHV, retrograde without complics
- Discharge POD #3
- Continues to do well - marked lifestyle improvement!!!



# Transcatheter AVR Technologies

**Transcatheter  
AVR**

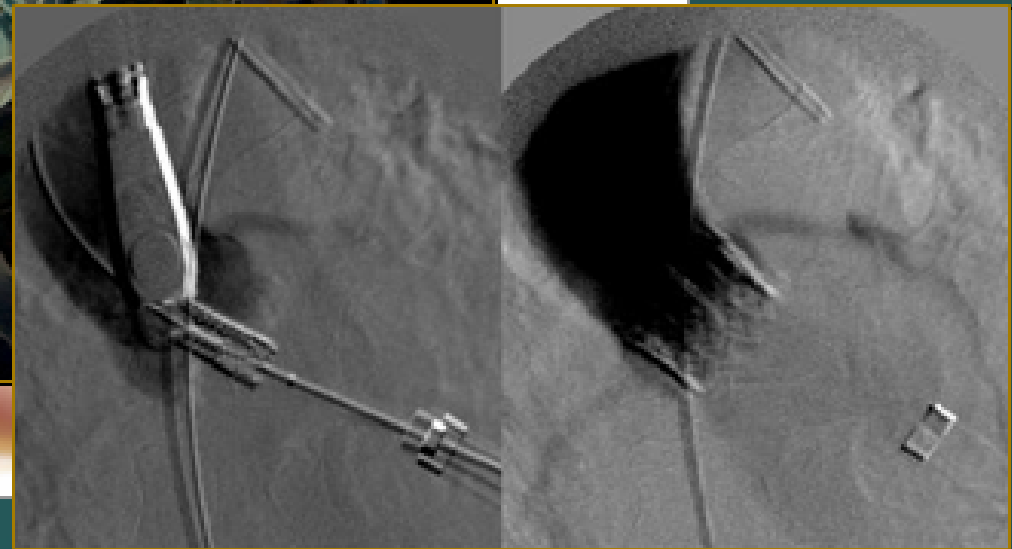
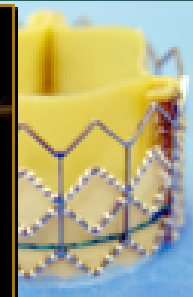
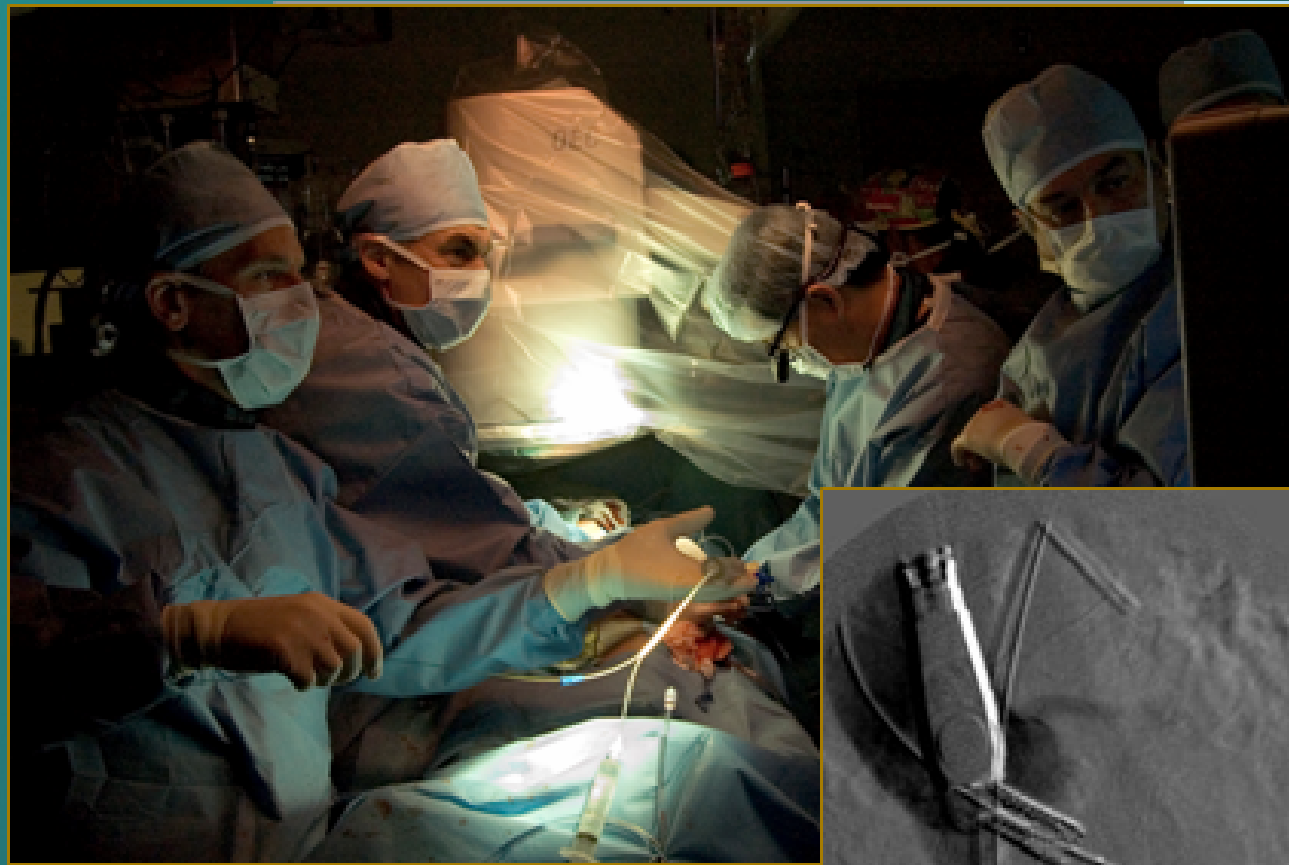
***Preferred***

- Poor vascular access
- Ao arch pathology (bulky atheroma or porcelain Ao)
- Retrograde AV crossing difficulties

**Trans-apical  
(OR)**

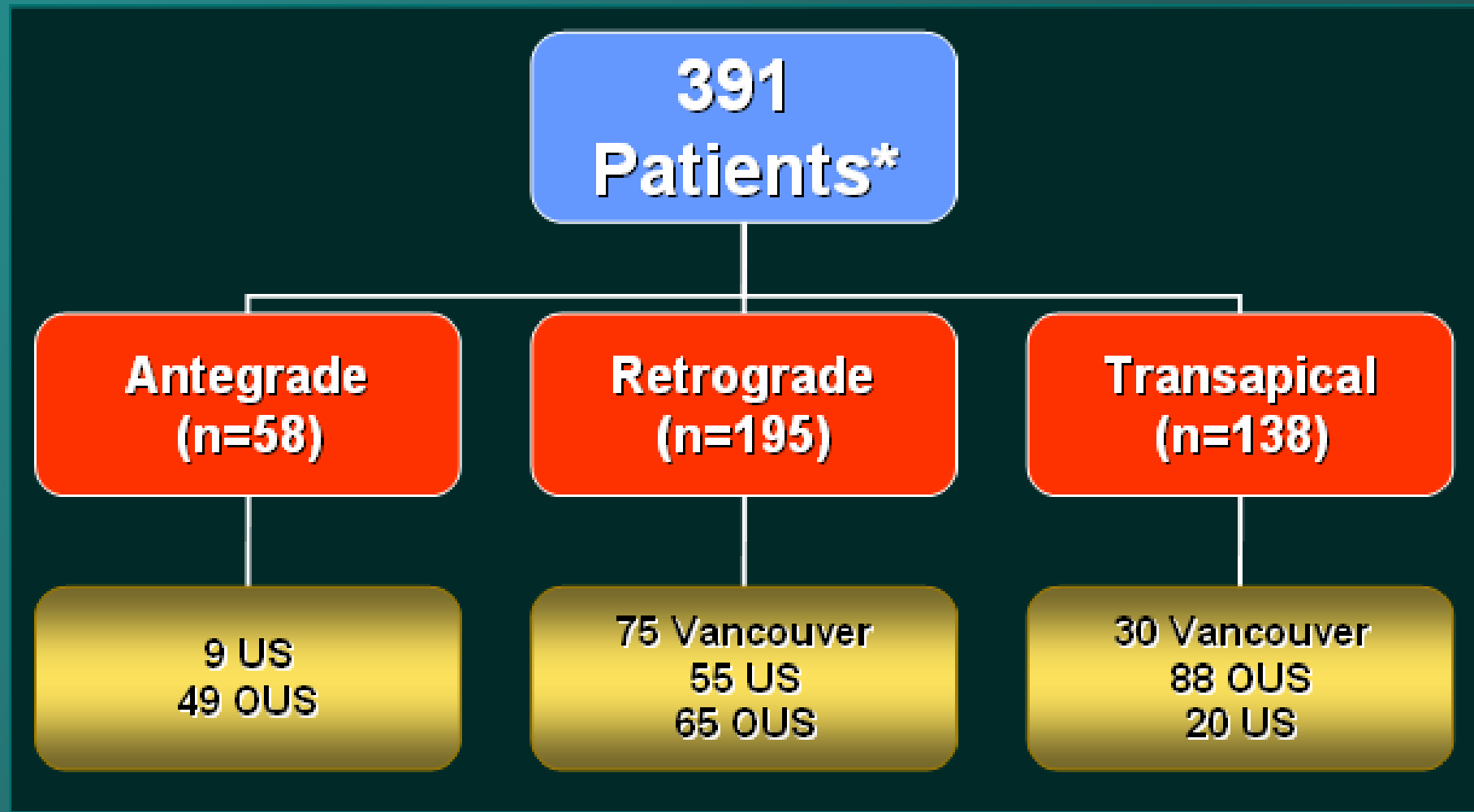


# Transapical Transcatheter AVR Implantation (Ascendra)





# Cribier-Edwards™ and Edwards SAPIEN™ THV\* Aortic Bioprosthesis Enrollment (March 22, 2007)

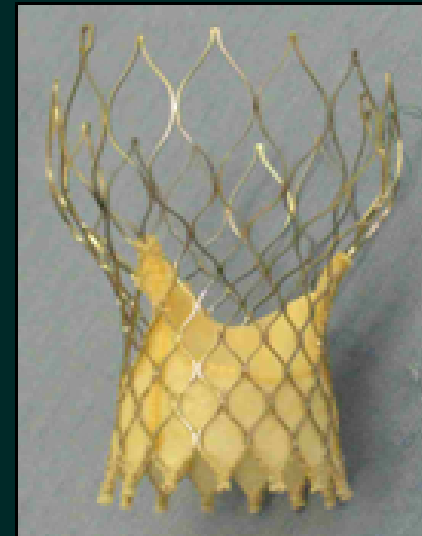
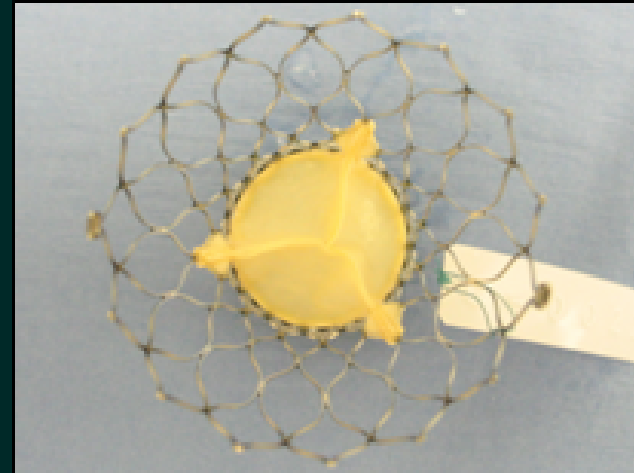


\* The Edwards SAPIEN™ valve incorporates bovine pericardial tissue and TFX™ treatment



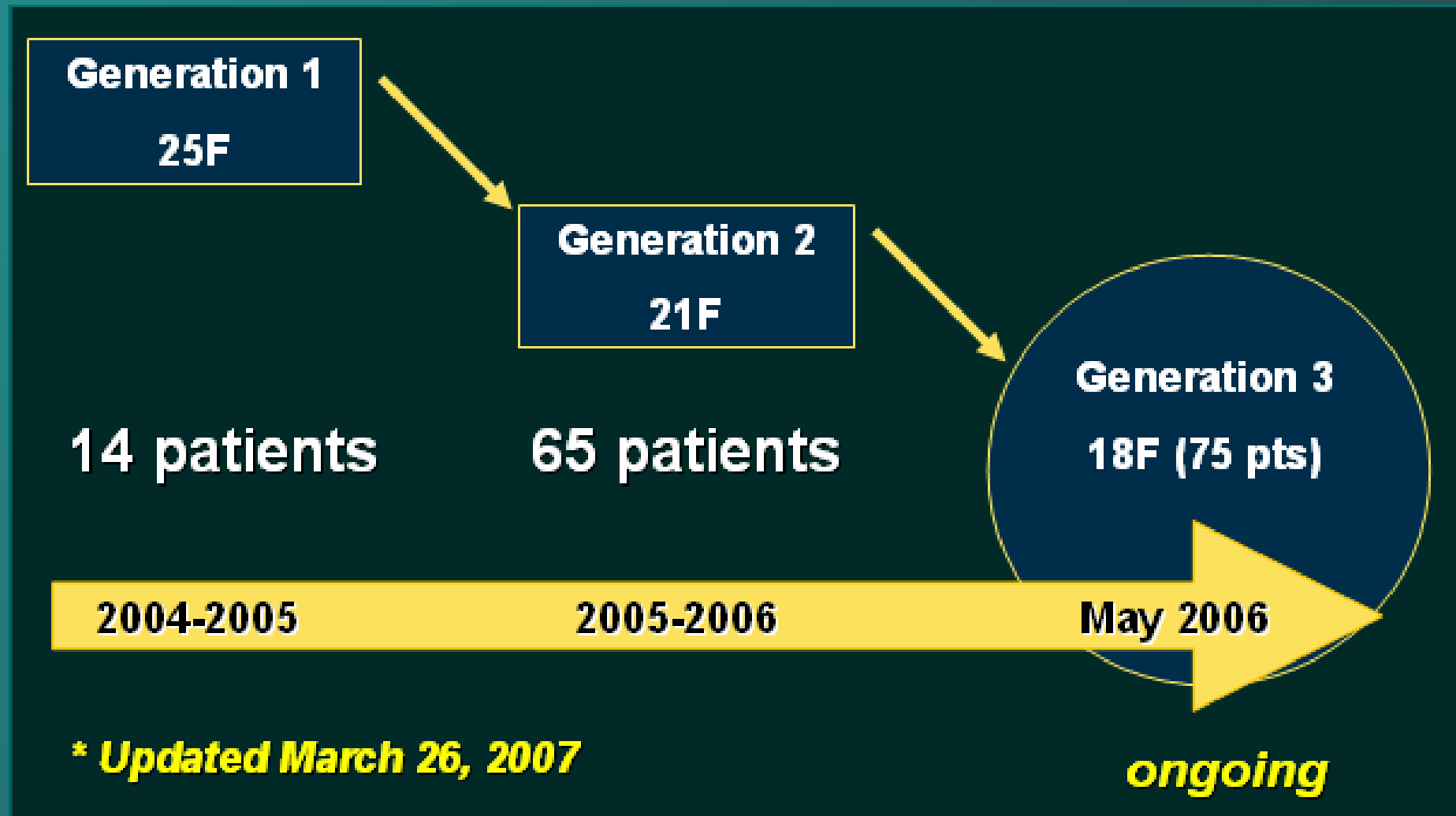
# tAVR: CoreValve

- FIM - E. Grube, J.C. Laborde
- Single layer porcine pericardium
- Tri-leaflet configuration
- Tissue valve sutured to frame
- Scalloped skirt
- Standard tissue fixation techniques
- 200M cycle AWT testing completed



# CoreValve Self-Expanding Bioprosthesis

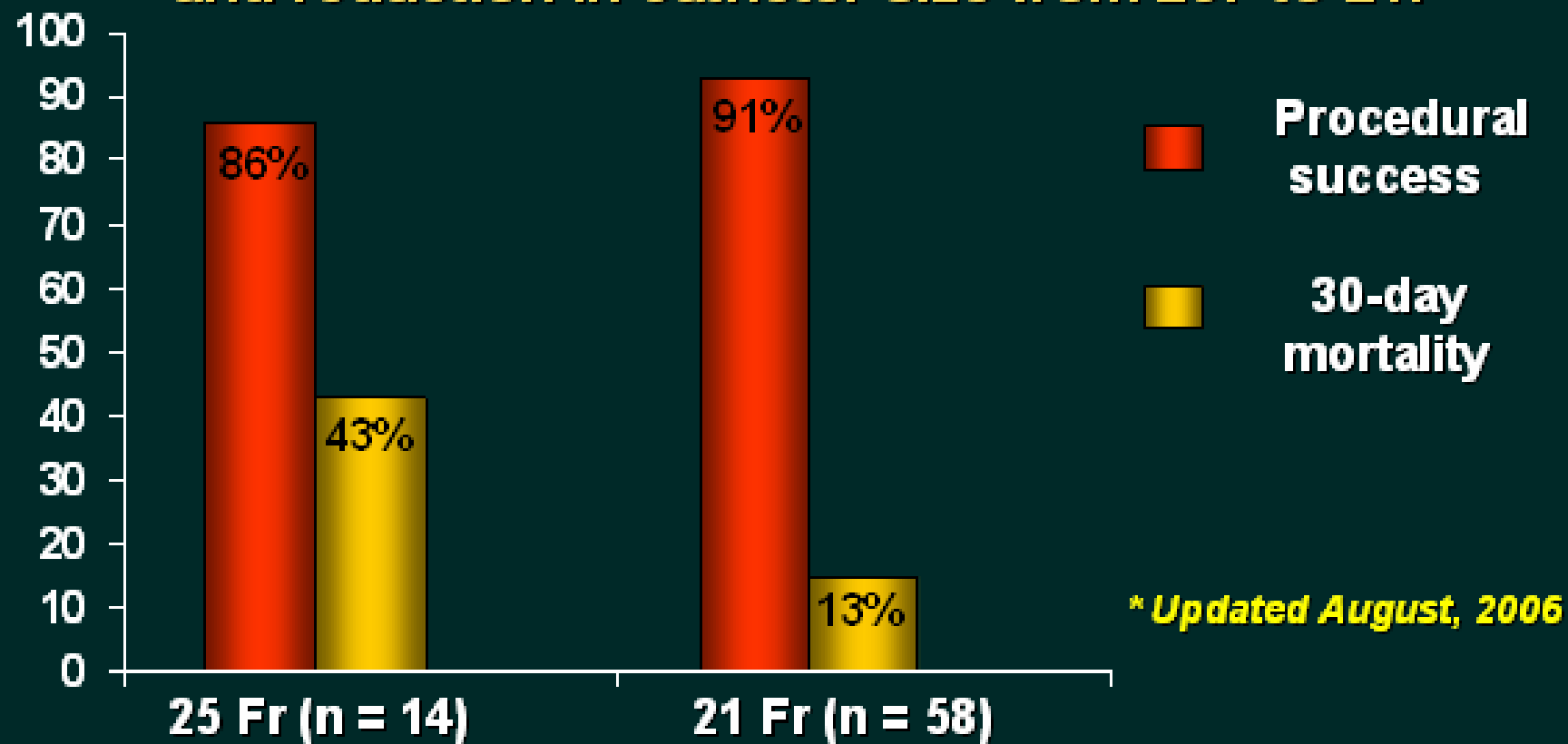
## *Clinical Experience: 154 Patients\**



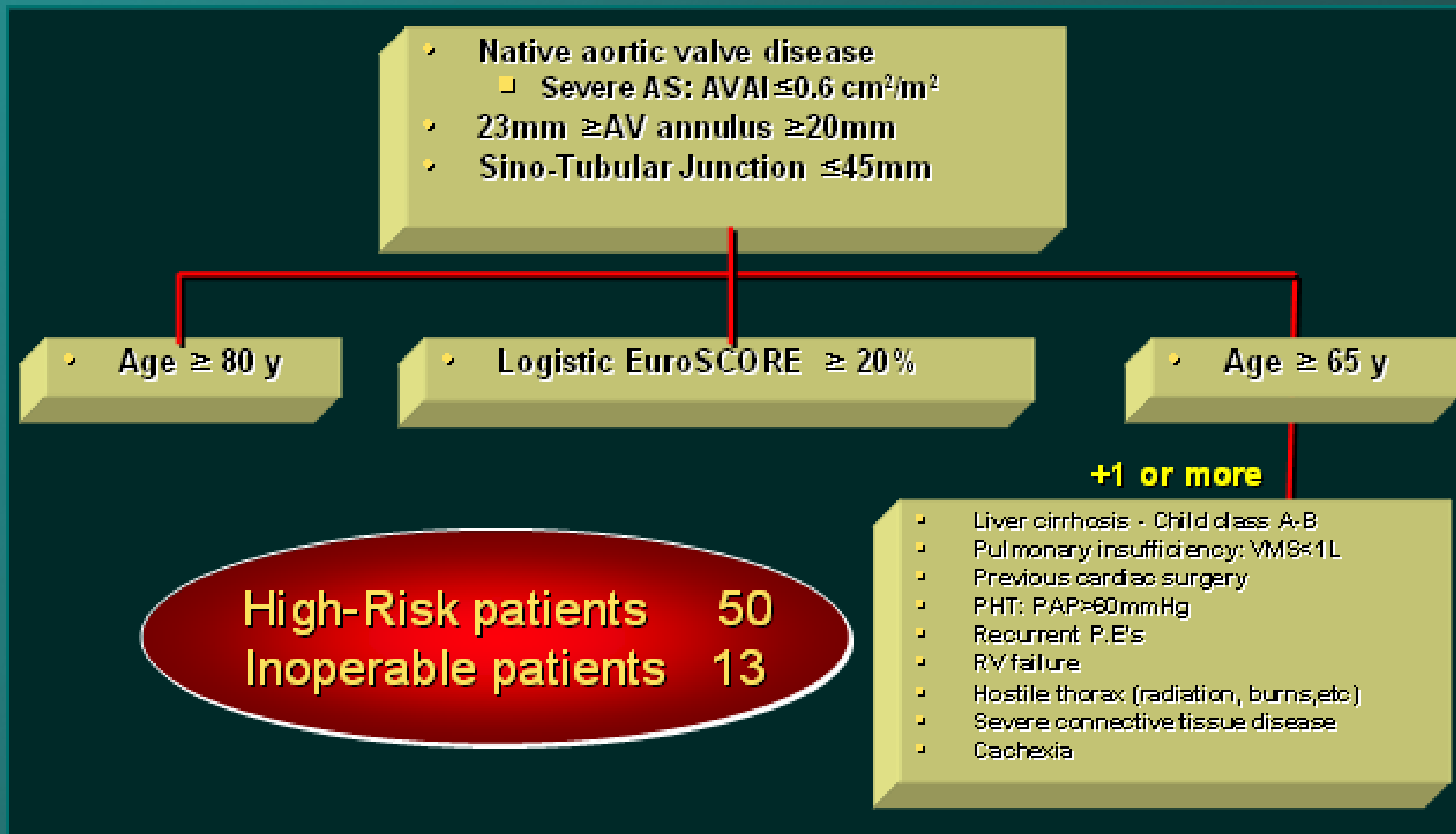
# CoreValve Self-Expanding Bioprosthesis

## *Clinical Experience: 72 Patients\**

Improved results with increased operator experience  
and reduction in catheter size from 25F to 21F



# CoreValve 21F Experience



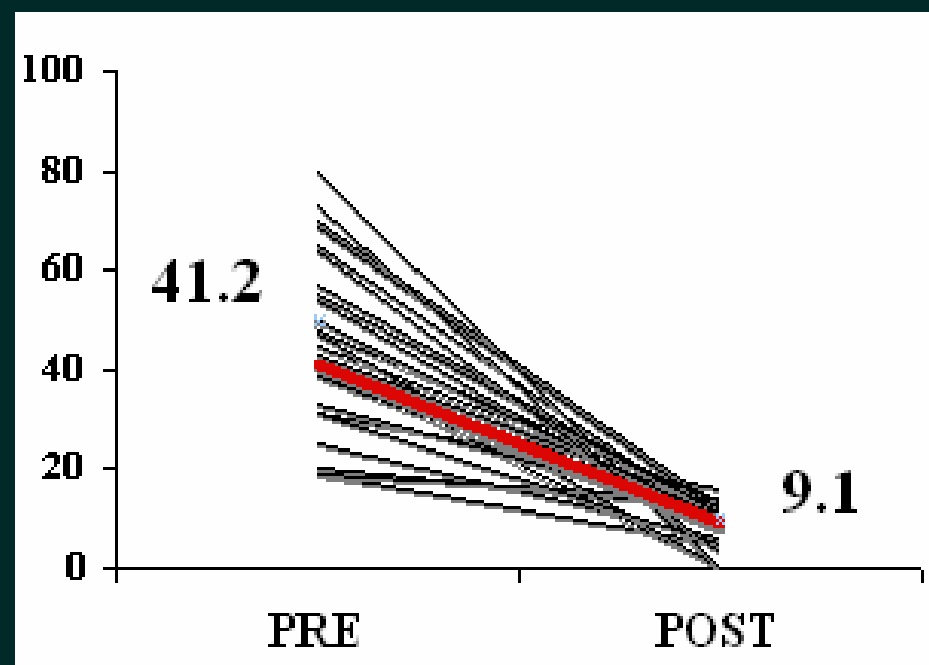
# CoreValve 21F Experience

## *Post-procedure Result (TEE)*

N=57

Mean gradient Post ( mm Hg)  
 $9.1 \pm 4.5$  [0-19]

ASA (cm<sup>2</sup>)  
 $1.59 \pm 0.40$  [1.1-2.3]



# CoreValve 21F Experience

## *Post-procedure Result (TEE)*

**N=57**

### Paravalvular leak

<b>0</b>	<b>18</b>	<b>31 %</b>
<b>I</b>	<b>29</b>	<b>51 %</b>
<b>II</b>	<b>9</b>	<b>16 %</b>
<b>III/IV</b>	<b>1*</b>	<b>2 %</b>

**\* Type A Aortic dissection**



# CoreValve 21F Experience:

## *In-Hospital Major Complications*

	<b>High-Risk (N=50)</b>	<b>Inoperable (N=13)</b>	<b>Overall (N=63)</b>
<b>logistic EUROSCORE</b>	23.4%	31.6%	25.4%
<b>In-hospital mortality</b>	8.0% (4)	30.8% (4)	12.7% (8)
<b>Conversion to surgery</b>	8.0% (4)*	-	6.4% (4)
<b>Discharged and well</b>	86% (43)	54% (7)**	80% (50)
<b>Discharged inclusive of surgery &amp; BAV only</b>	87% (55)		

\* High risk group: 1 converted patient died

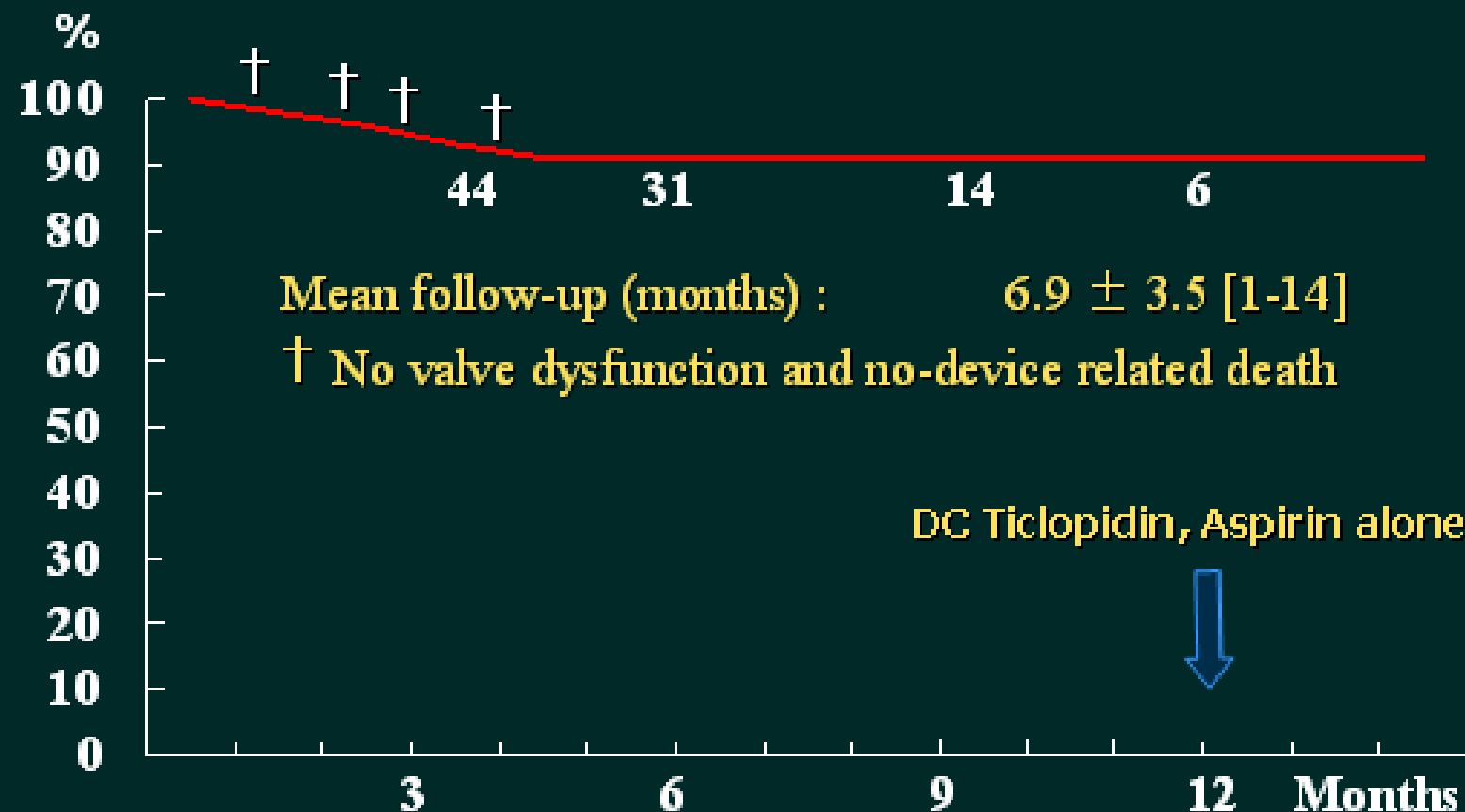
\*\* Inoperable group : 2 patients had BAV alone – intent to treat





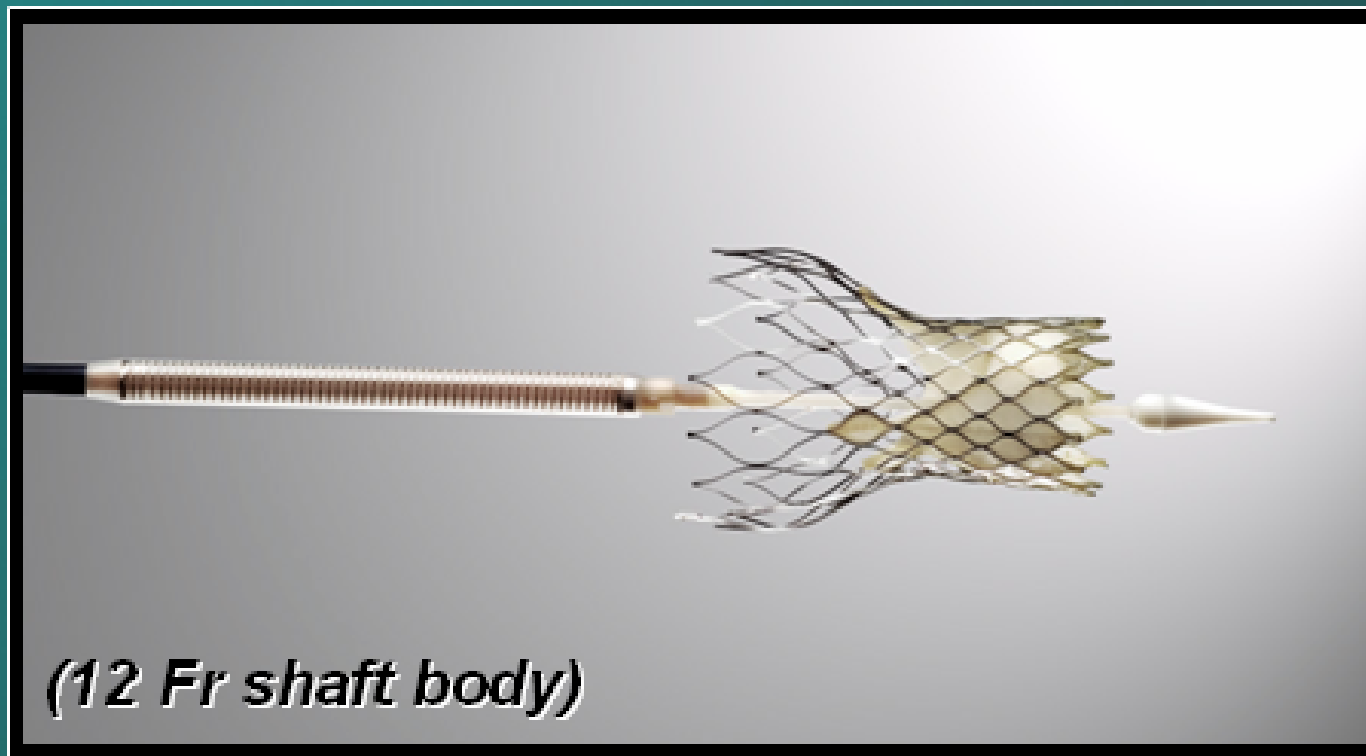
# CoreValve 21F Experience

## *Lifetable Analysis (n=50)*



# CoreValve ReValving™ System

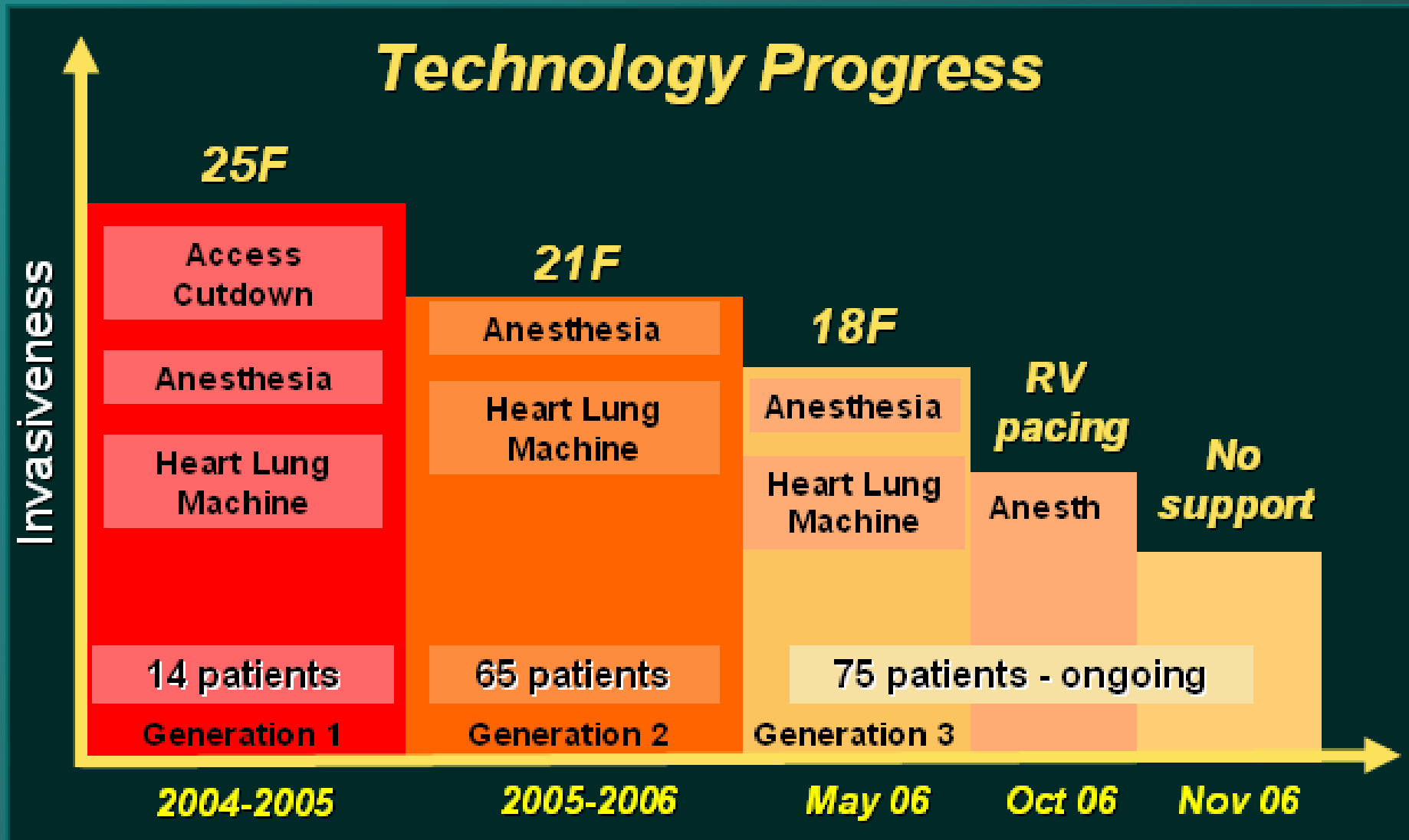
## *18 Fr Delivery System*



***Self-expanding nitinol frame, porcine pericardial valve, and 18 Fr sheathed delivery system***



# CoreValve ReValving™ System



# CoreValve Study - 3 Center Experience\* 21F and 18 F

## Baseline Characteristics

<b>Number of Patients</b>	<b>N=86</b>	<b>N=50 (21F)</b>	<b>N=36 (18F)</b>
Age (years $\pm$ SD)	82.2 $\pm$ 5.9	81.3 $\pm$ 5.2	83.4 $\pm$ 6.7
NYHA III/IV	71 [83]	43 [86]	28 [77]
LVEF, %, mean	54 $\pm$ 16	52 $\pm$ 18	57 $\pm$ 14
Logistic EuroSCORE, %, mean $\pm$ SD	21.7 $\pm$ 12.6	23.4 $\pm$ 13.5	19.1 $\pm$ 11.1
Peak gradient, mmHG, mean $\pm$ SD	70.9 $\pm$ 22.8	66.0 $\pm$ 18.8	78.3 $\pm$ 26.0
Aortic valve area, cm <sup>2</sup> , mean $\pm$ SD	0.60 $\pm$ 0.16	0.66 $\pm$ 0.19	0.54 $\pm$ 0.15

\*Siegburg, Leipzig, and Montreal



# CoreValve Study - 3 Center Experience\*

## 21F and 18 F

### 30 Day Outcomes

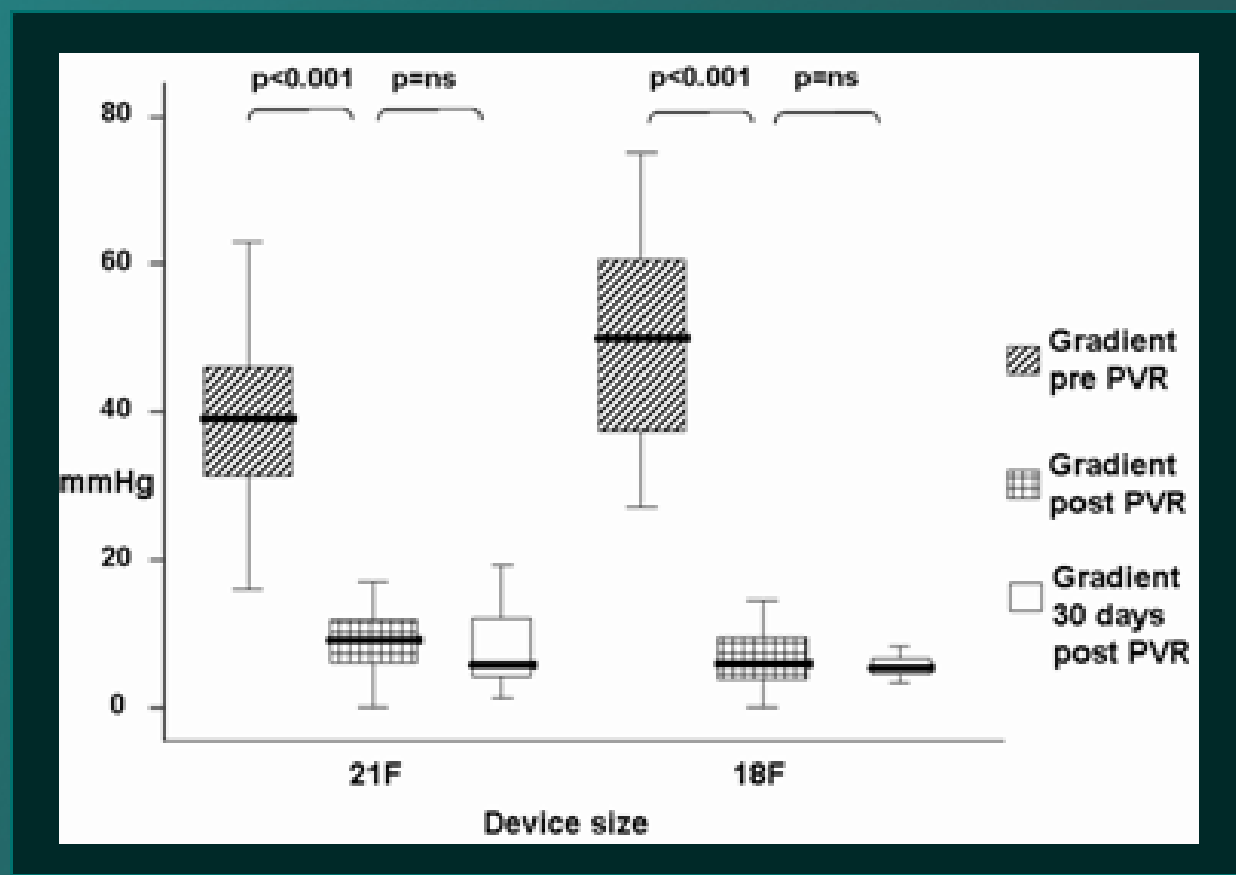
	Overall	21 Fr	18 Fr
<i>patients with acute device success</i>	<i>N=76</i>	<i>N=44</i>	<i>N=32</i>
Death, n [%]	7 [9]	3 [7]	4 [13]
- Cardiovascular death, n [%]	6 [8]	3 [7]	3 [9]
MI, n [%]	1 [1]	1 [2]	0
Stroke, n [%]	7 [9]	4 [9]	3 [9]
Cardiac tamponade, n [%]	4 [4]	1 [2]	3 [9]
Overall MACCE, n [%]	19 [25]	9 [20]	10 [31]

\*Siegburg, Leipzig, and Montreal



# CoreValve Study - 3 Center Experience\* 21F and 18 F

## AV Gradients



\*Siegburg, Leipzig, and Montreal



# Transcatheter AVR

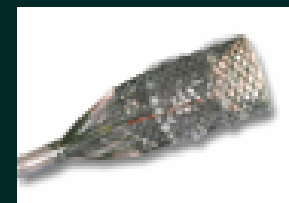
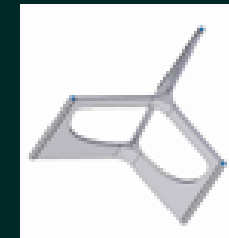
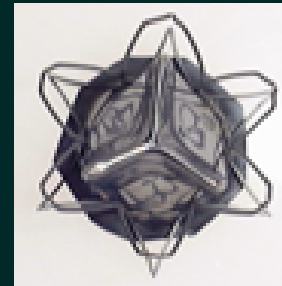
## The Future and Conclusions...



# Future Aortic Valve Concepts

- **Other stent-valve designs**

- Bonhoeffer (bovine jugular vein)
- AorTech
- Paniagua (EndoTech)
- 3F (apical)
- Palmaz-Bailey (nanotech-nitinol)
- Direct Flow
- AorTx
- Sadra Lotus valve

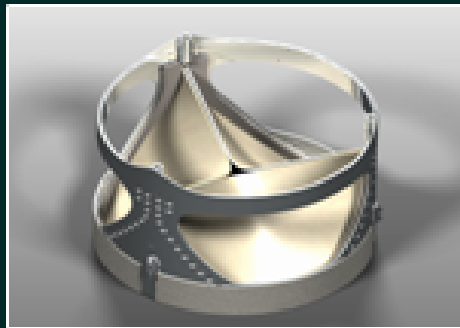




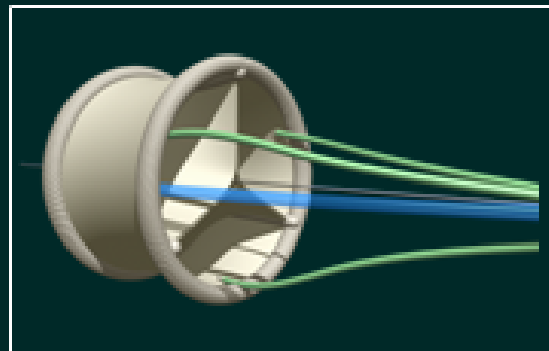
# Transcatheter Valve Therapy

## *Next Generation Devices*

*Lower profile, repositionable, less pAR*



AorTx



DirectFlow



Sadra



# What's in a Name?

Placement of **AoRTic** Tra**N**scathet**ER**  
Valves



# Evolution of "PARTNER" Trial DESIGN

## **PARTNER EU**

**Multi-center, multi-national,  
single arm, prospective,  
consecutive, stratification  
10 Sites, 8 countries  
6 month enrollment period**

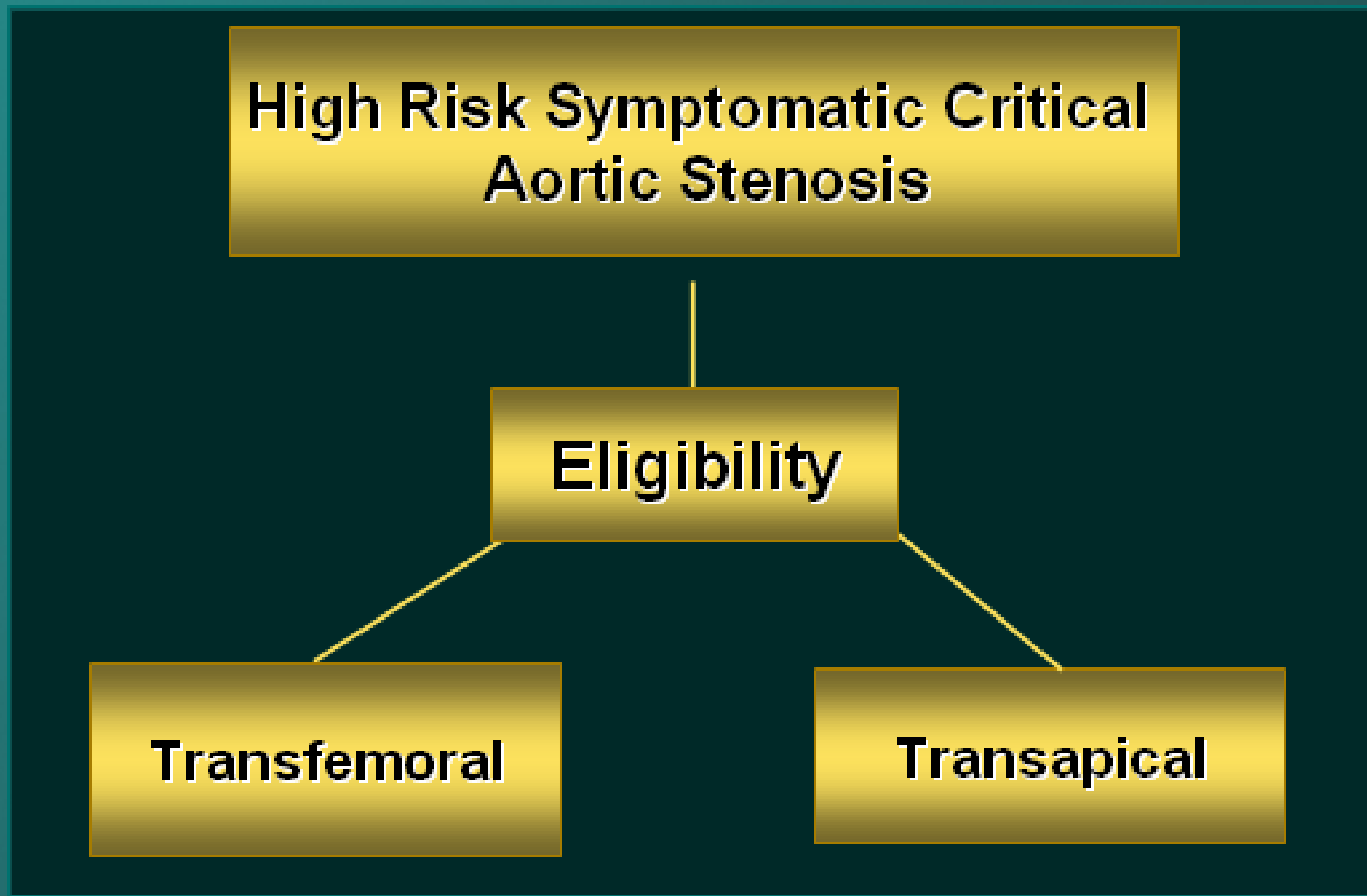
## **PARTNER US**

**Multi-center, stratified  
Randomized controlled trial  
15 sites, US  
18 month enrollment period**

***Overlapping and common objectives***

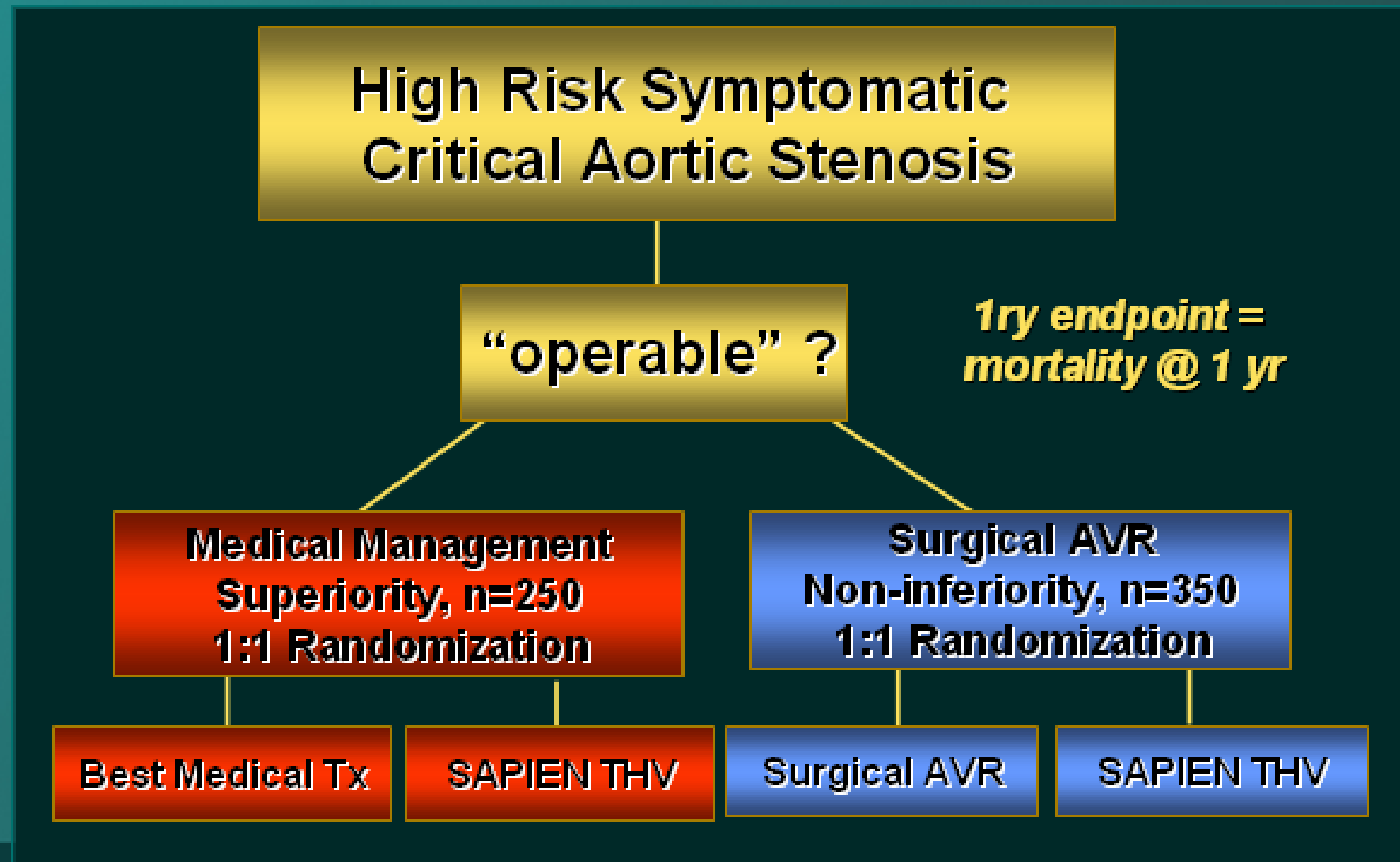


# PARTNER EU, Non-randomized Trial - 125 Patients



# PARTNER US, Randomized Trials

## Total = 600 Patients



# ***FUTURE*** Candidates for Transcatheter AVR

**Severe AS**

***ACC/AHA Class I and IIa  
(Symp and Asymp)***

**Normal and High  
Surgical Risk**

**AR  
patients**

**tAVR  
+ PCI**

**tAVR  
+ MR Rx**

**Failed  
AVR**



# Transcatheter AVR

## Conclusions & Observations - 1

- The early generation tAVR systems have been studied in multicenter international clinical trial registries to iterate device concepts and refine operator techniques (total # patients Edwards + CoreValve ~ 550).
- In these studies, “very high risk” patients were subjected to technically challenging and evolving interventional procedures.
- Nevertheless, feasibility of tAVR has been demonstrated with both the balloon-expandable and the self-expanding systems.



# Transcatheter Valve Therapy

## *Aortic Stenosis*

### *First Generation Devices*



Cribier-Edwards  
391 patients



CoreValve  
154 patients





# Transcatheter AVR

## Conclusions & Observations - 2

- Short-term hemodynamic results have been consistently excellent!
- The antegrade approach is challenging and complication-prone; requires superior technical skills and an experienced team.
- The retrograde approach is easier, but is limited by vascular access; newer systems will have lower profiles (<20 Fr).
- The trans-apical approach is very promising and provides a rapid sternal-sparing, beating heart solution to AVR in high risk patients.



# Transcatheter AVR

## Conclusions & Observations - 3

- Clearly, larger valve sizes (e.g. 26mm PHV) are needed to accommodate all patients and to prevent/reduce para-valvular regurgitation.
- Mid-term clinical outcomes are encouraging with no out-of-hospital valve failures (>100 pts with >6 mos FU thusfar)!
- Late valve function and clinical outcomes data are sorely needed to assess valve durability.
- Successful tAVR programs require a cohesive multi-disciplinary team, including close collaboration with cardiac surgery.



# Transcatheter AVR

## Conclusions & Observations - 5

- Next generation tAVR technologies will incorporate innovative device design concepts, lower profile systems, and the potential for recovery and repositioning to optimize implantation and placement.
- **NOW** is the time for a randomized clinical trial in high surgical risk AS patients, comparing tAVR systems with appropriate control therapies...the outcomes of these important studies will determine the future role of tAVR in patients with severe AS!

