

Overview Of Percutaneous Valve Therapy

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, GDS

Stockholder or other Equity:
Sadra, GDS, Mitralign



Transcatheter Valve Therapy (TVT)

Predicting the Future



***Transcatheter
valve therapy is the
MOST EXCITING
new procedure in the
field of interventional
cardiovascular
therapeutics!!!***



First successful percutaneous valve replacement!

- Case report: 12-year old boy with pulmonary insufficiency and stenosis on a prosthetic conduit implanted for pulmonary atresia at age 4
- Successful implantation of an 18 mm bovine jugular vein with its native valve connected to a platinum stent
- Partial relief of the stenosis and excellent valve competence; no procedural complications

Bonhoeffer et al, The Lancet, Oct 2000



Transcatheter Valve Therapy

**Is there really a large
pool of patients with
mod/severe VHD who
are “untreated”?**



Do patients with valvular heart disease receive treatment according to established guidelines?



ELSEVIER

A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease

31.8% did not undergo intervention, despite NYHA class III/IV symptoms

lung^{a*}, Gabriel Baron^b, Eric G. Butchart^c, François Delahaye^d,
Hilke-Bärwolf^e, Olaf W. Levang^f, Pilar Tornos^g,
Vanoverschelde^h, Frank Vermeerⁱ, Eric Boersma^j,
avaud^b, Alec Vahanian^a

Aims To identify the characteristics, treatment, and outcomes of contemporary patients with valvular heart disease (VHD) in Europe, and to examine adherence to guidelines.
Methods and results The Euro Heart Survey on VHD was conducted from April to July 2001 in 92 centres from 25 countries; it included prospectively 5001 adults with moderate to severe native VHD, infective endocarditis, or previous valve intervention. VHD was native in 71.9% of patients and 28.1% had had a previous intervention. Mean age was 64±14 years. Degenerative aetiologies were the most frequent in aortic VHD and mitral regurgitation while most cases of mitral stenosis were of rheumatic origin.

Coronary angiography was used in 85.2% of patients before intervention. Of the 1269 patients who underwent intervention, prosthetic replacement was performed in 99.0% of aortic VHD, percutaneous dilatation in 33.9% of mitral stenosis, and valve repair in 46.5% of mitral regurgitation; 31.7% of patients had ≥1 associated procedure. Of patients with severe, symptomatic, single VHD, 31.8% did not undergo intervention, most frequently because of comorbidities. In asymptomatic patients, accordance with guidelines ranged between 66.0 and 78.5%. Operative mortality was <5% for single VHD.

Conclusions This survey provides unique contemporary data on characteristics and management of patients with VHD. Adherence to guidelines is globally satisfying as investigations and interventions.

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Cardiology Department, Bichat Hospital, 46 rue Henri Huchard, 75018 Paris, France.

12
is.fr (B. lung).

- 92 hospitals from 25 countries
- 5,001 patients from April-July, 2001



Euro Heart Survey on VHD:

***31.8% of patients were not operated,
despite NYHA class III/IV Sx***

- ***CARDIAC REASONS***

- decrease Sx after treatment 45%
- “end-stage” cardiac disease 30%

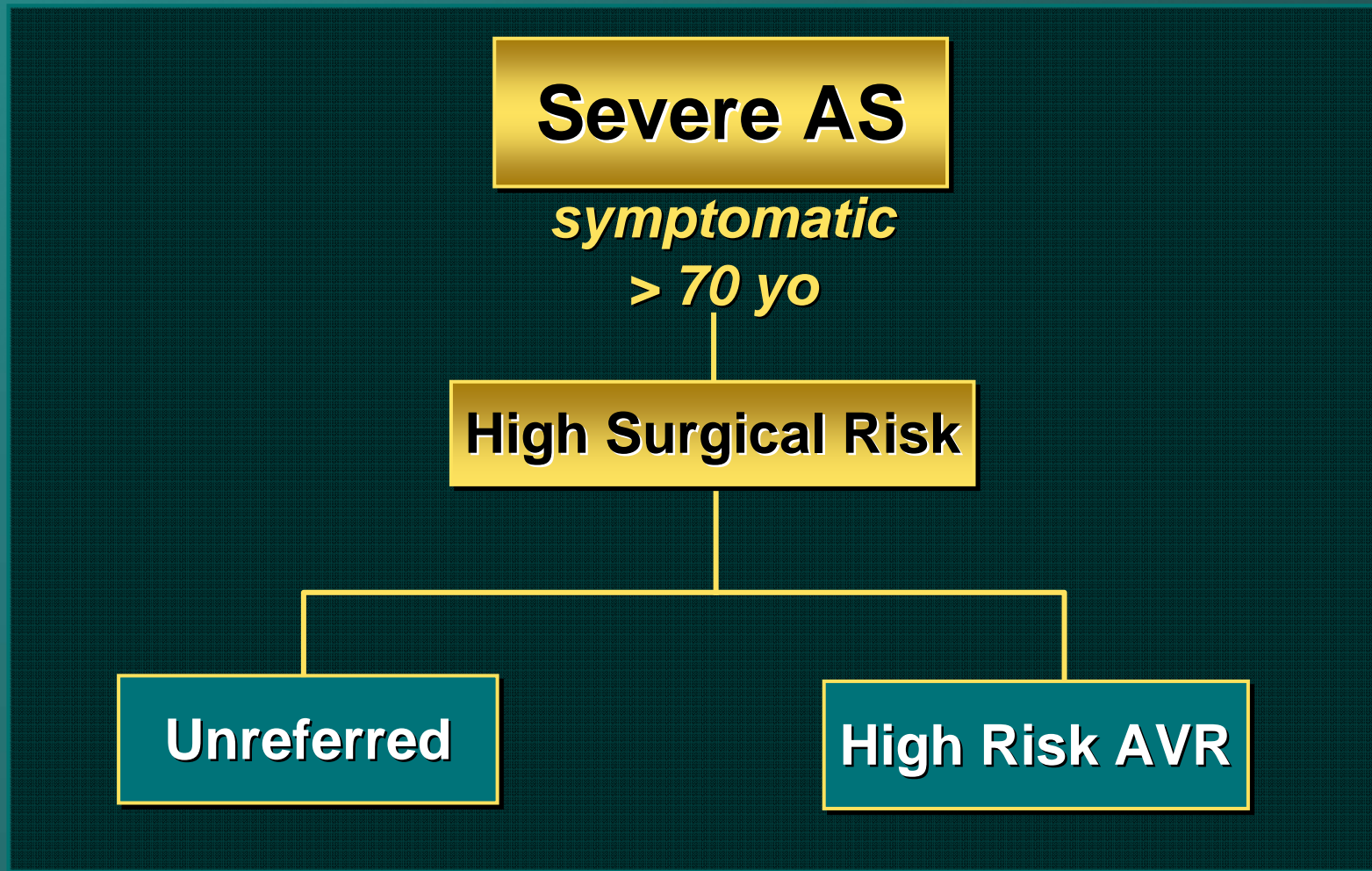
- ***EXTRA-CARDIAC REASONS***

- age 27%
- co-morbidities 27%
- patient refusal 16%

Transcatheter Valve Therapy

- ***For stenotic valves***
 - Pulmonary (or valve conduit) stenosis (a/o regurgitation)
 - ***Aortic stenosis***
 - Mitral stenosis
- ***For regurgitant valves***
 - Aortic regurgitation
 - Mitral regurgitation

CURRENT Candidates for Transcatheter AVR



***High Risk* AVR Patients with Poor Outcomes**

- Radiation chest wall/heart disease
- Octogenarians with multiple co-morbidities
- STS Predicted Risk >10%, Logistic EuroSCORE >30% (~10-15% operative risk)
- Cirrhosis with portal hypertension
- ESRD on dialysis
- Porcelain aorta
- Degenerative neurocognitive dysfunction

***There is no perfect formula!
Requires some quantitative risk algorithm
+ a thoughtful surgeon/cardiologist!!!***

Potential tAVR Patients

SEVERE AORTIC STENOSIS

REFUSALS

“MEDICAL THERAPY”

“ASYMPTOMATIC”

BALLOON AORTIC
VALVULOPLASTY

There is an unmet clinical need!

AORTIC VALVE
REPLACEMENT
SURGERY

HIGH-RISK
PATIENTS



Transcatheter AVR

Technology Overview...

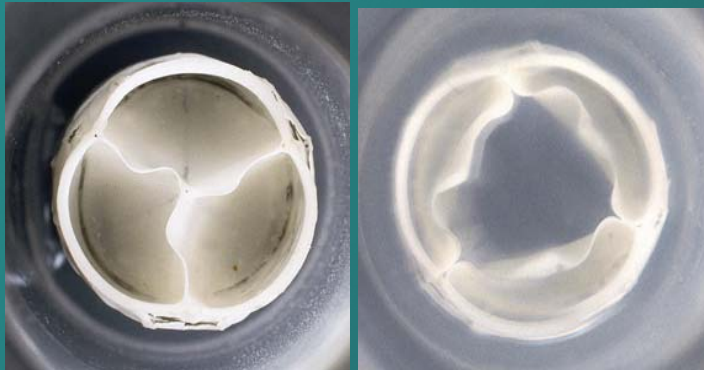


Transcatheter AVR Systems

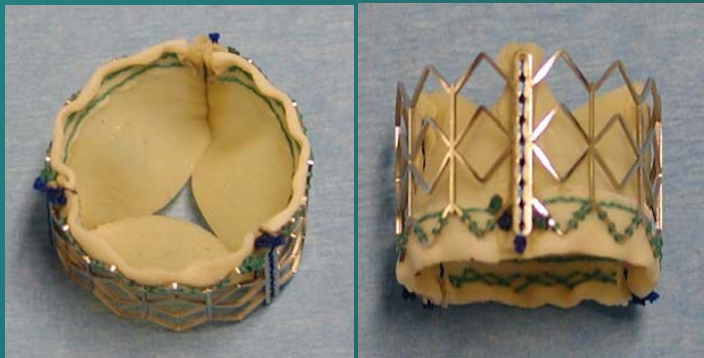
1st Generation

- **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



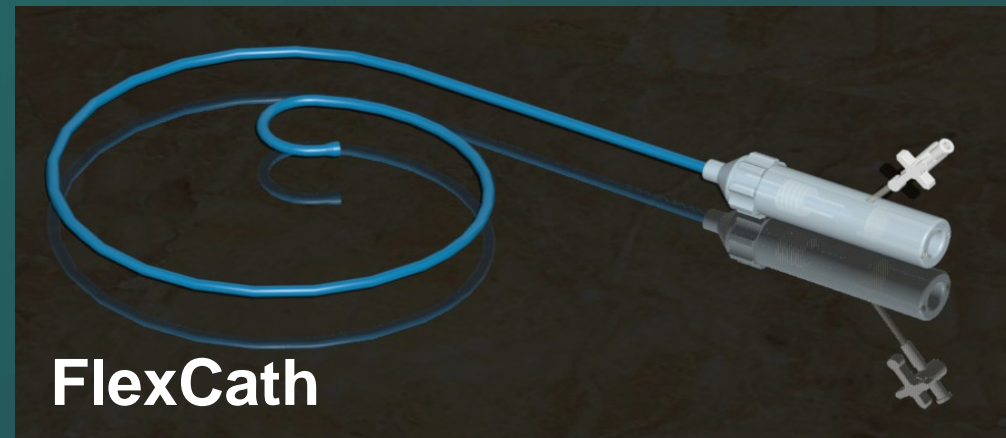
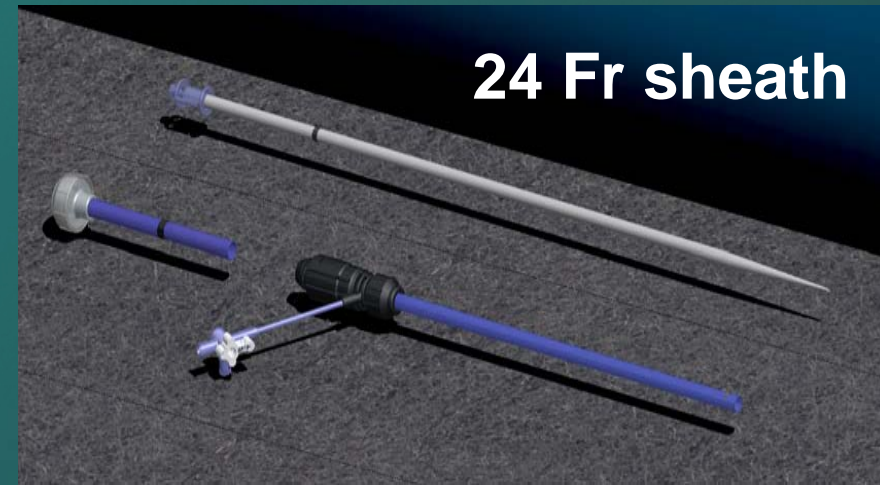
Second generation – bovine pericardium

Current Device



- equine pericardial valve
- stainless steel stent
- 23mm and 26mm diameters
- balloon-expandable
- AVA = 1.7-1.9 cm²

Cribier-Edwards Percutaneous Heart Valve **SYSTEM**



CoreValve ReValving™ System

4 Components



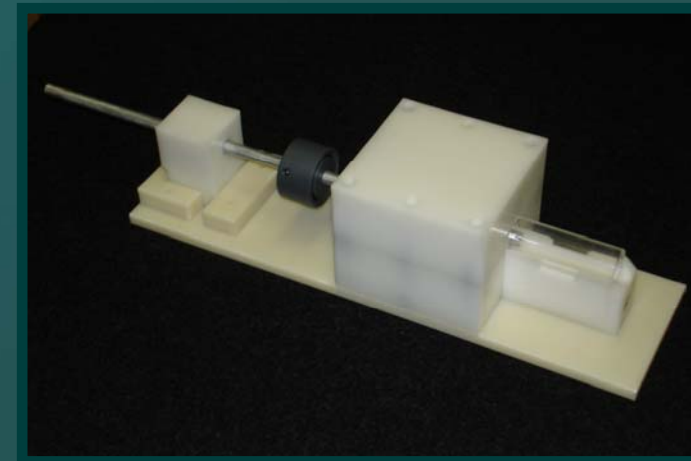
1. Self-expanding multi-level self-expanding nitinol frame



2. Porcine pericardial valve



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



4. Loading system



Transcatheter AVR

Early Clinical Results...



First successful percutaneous aortic valve replacement!

Alain Cribier



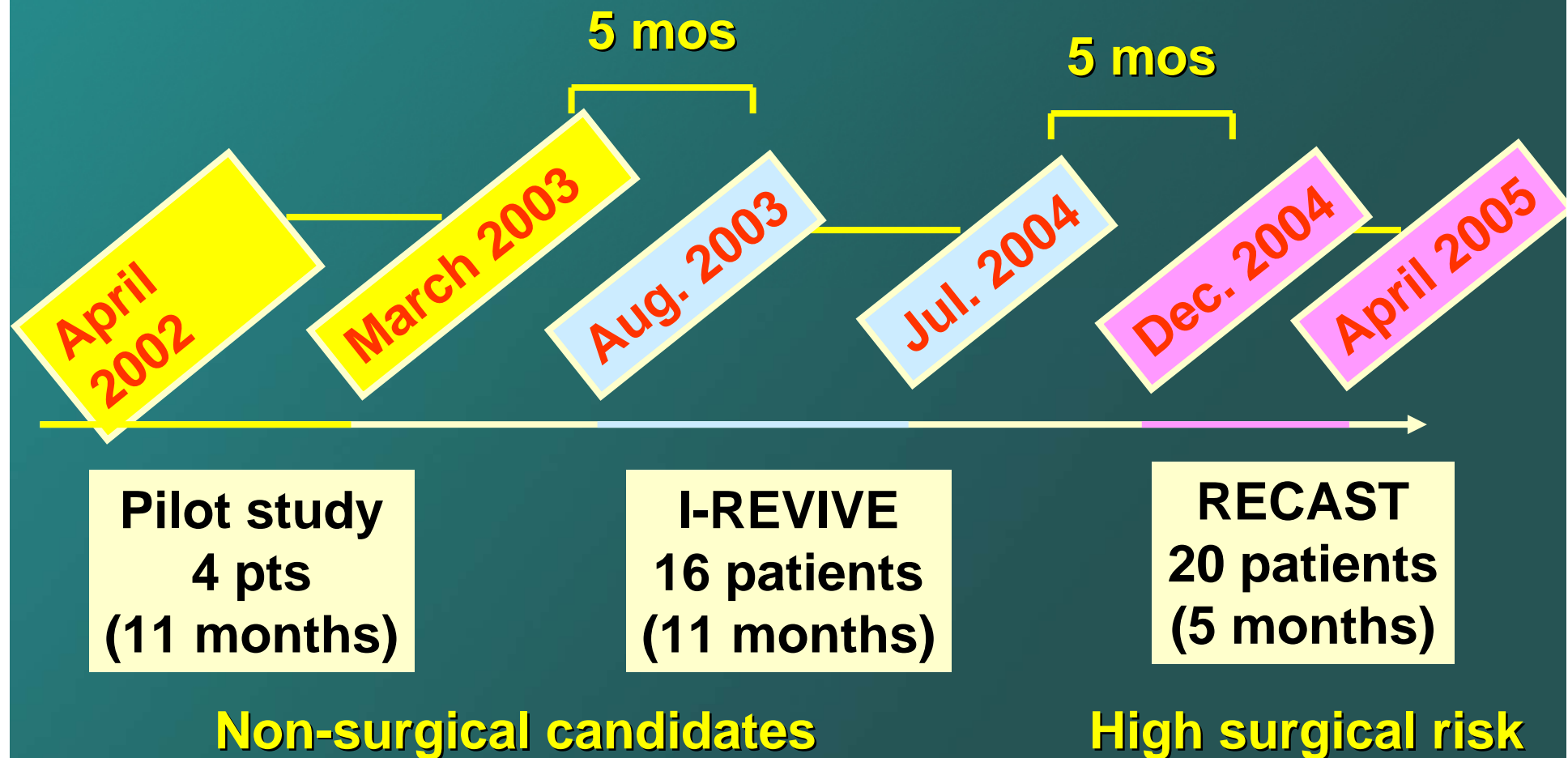
April 16, 2002

Day 8 post-implantation



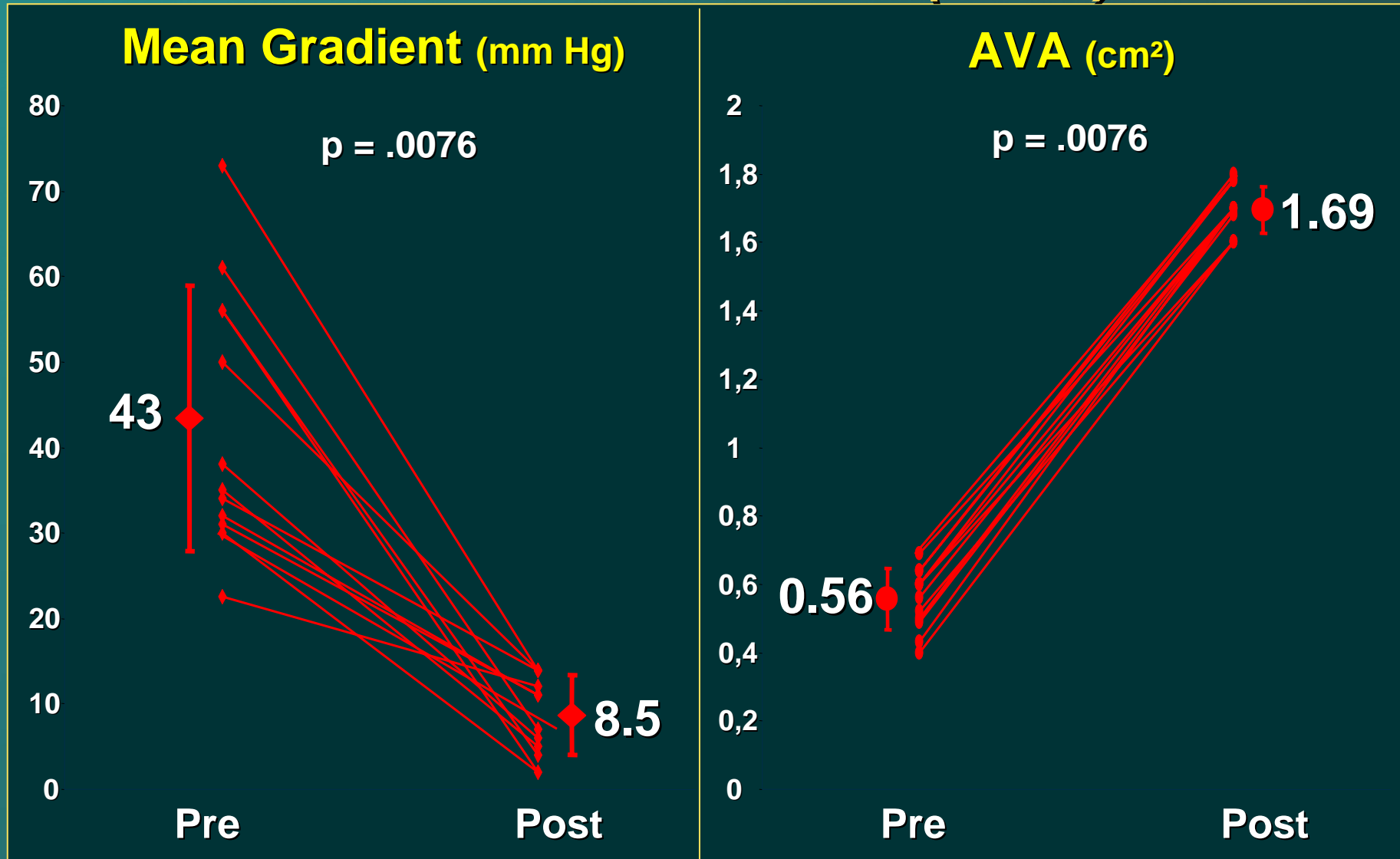
Cribier – Early PHV Experiences

Rouen, France



Cribier – Early PHV Experiences

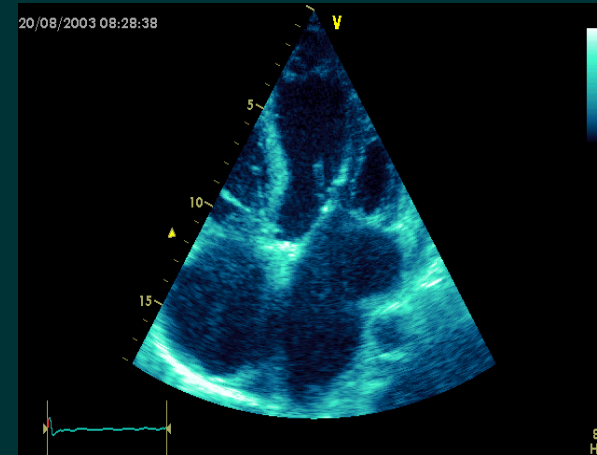
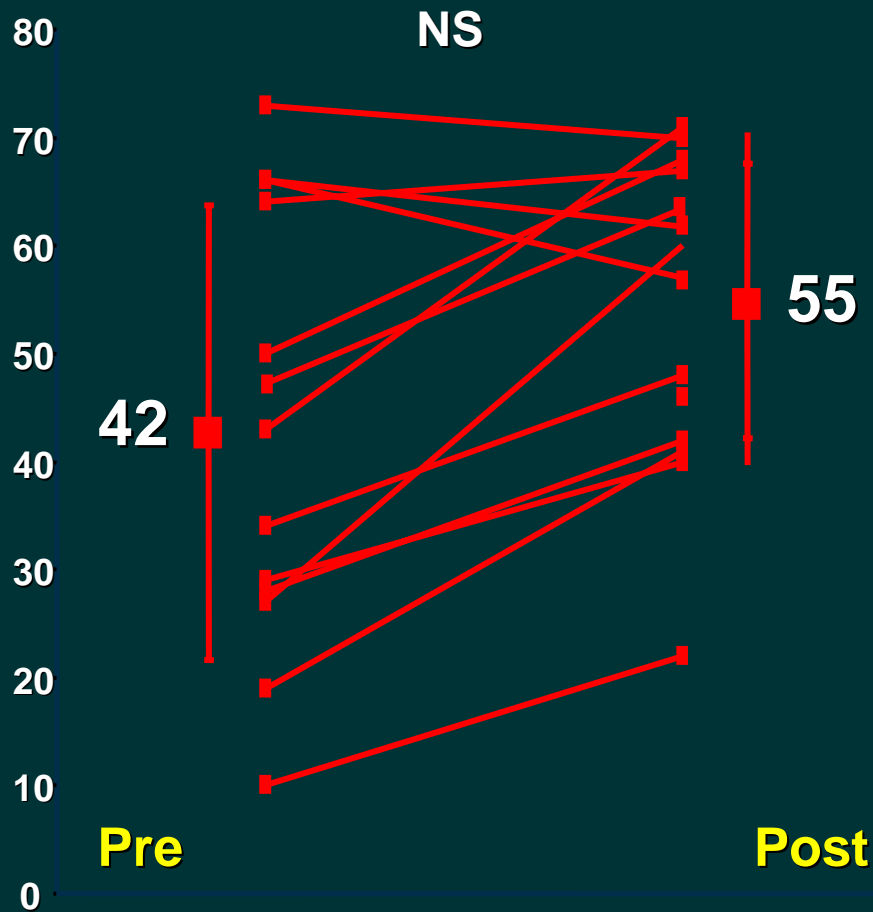
Procedural Results (n=16)



Cribier – Early PHV Experiences

Changes in LVEF (n=13)

Ejection Fraction (%)



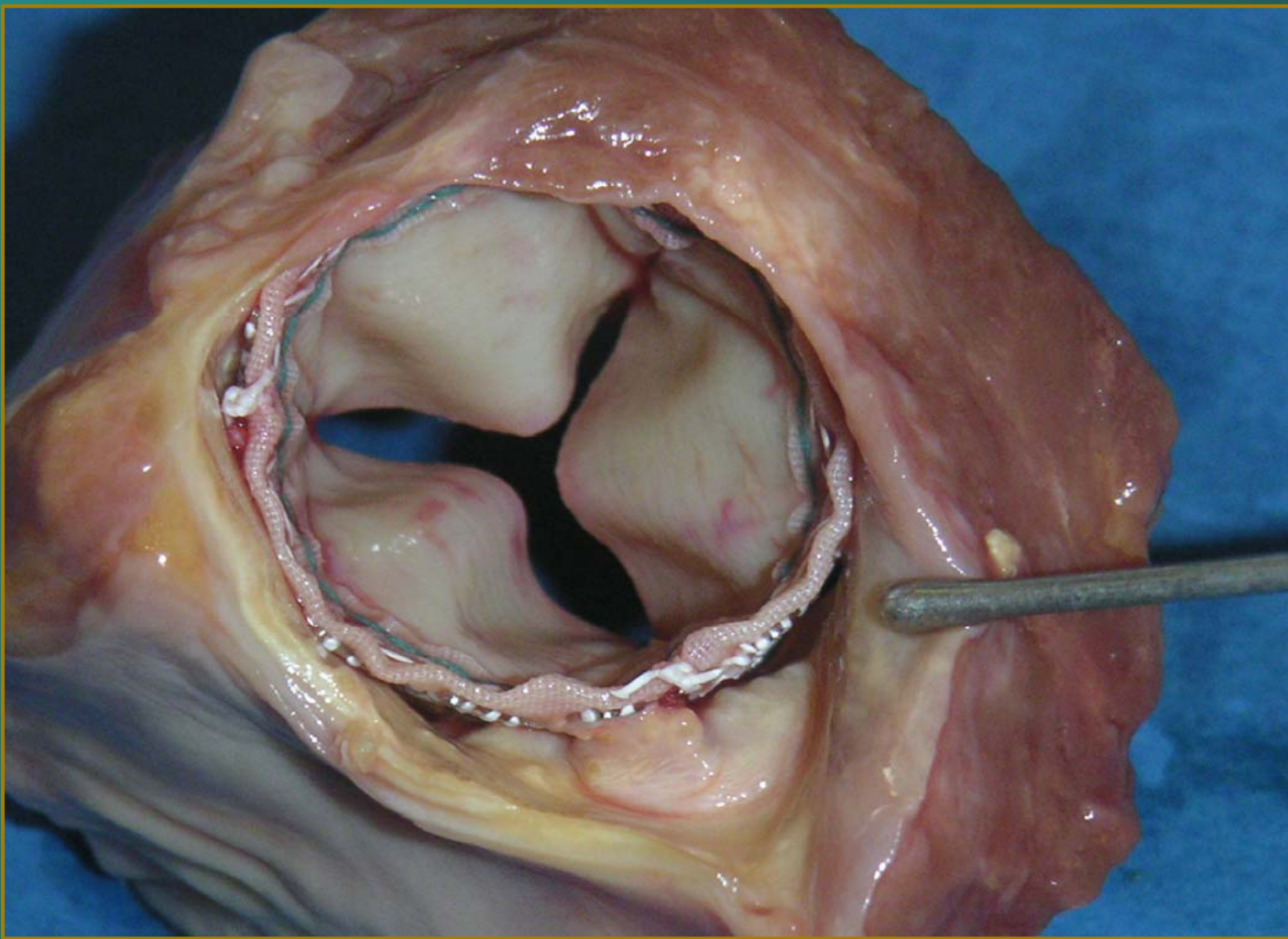
Baseline: EF 20%



8 days post PHV: EF=58%



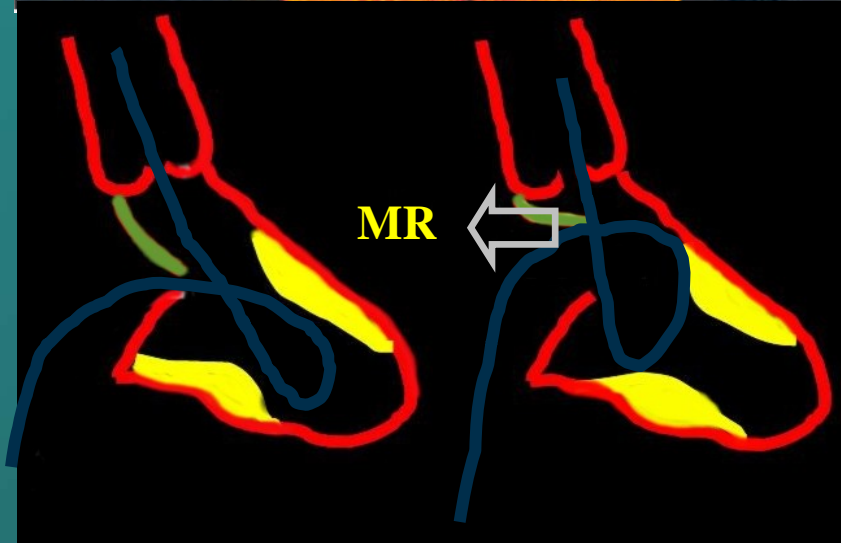
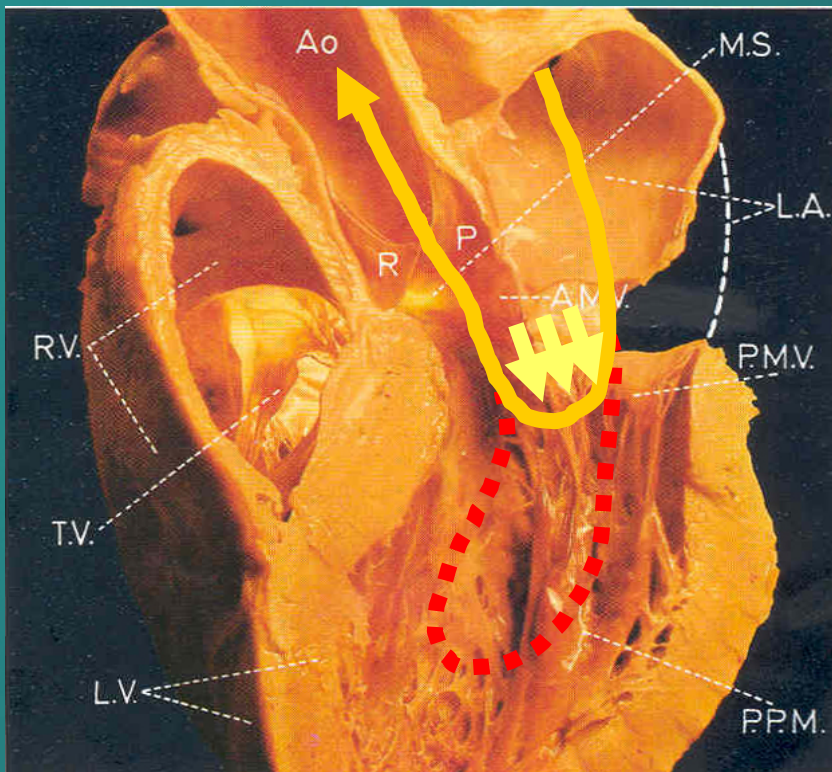
Para-valvular Regurgitation



Patient #5



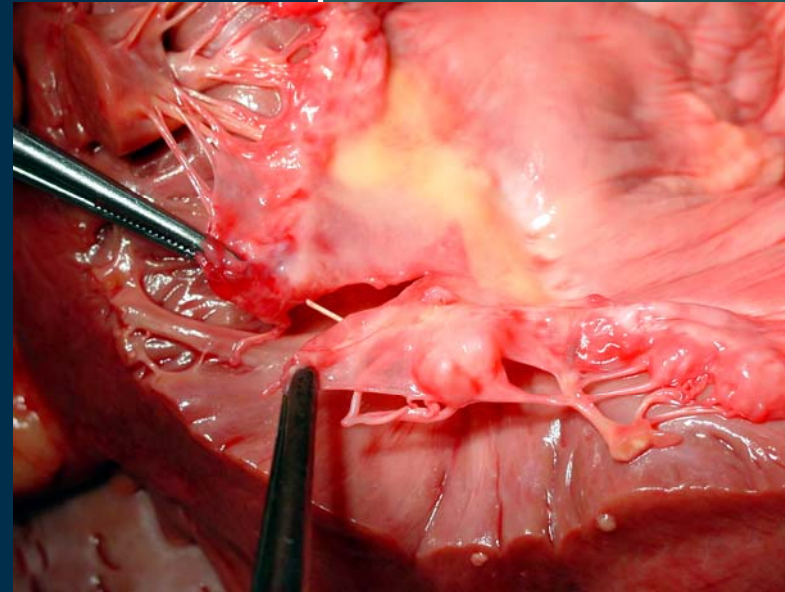
Antegrade Approach: Guidewire Position in LV



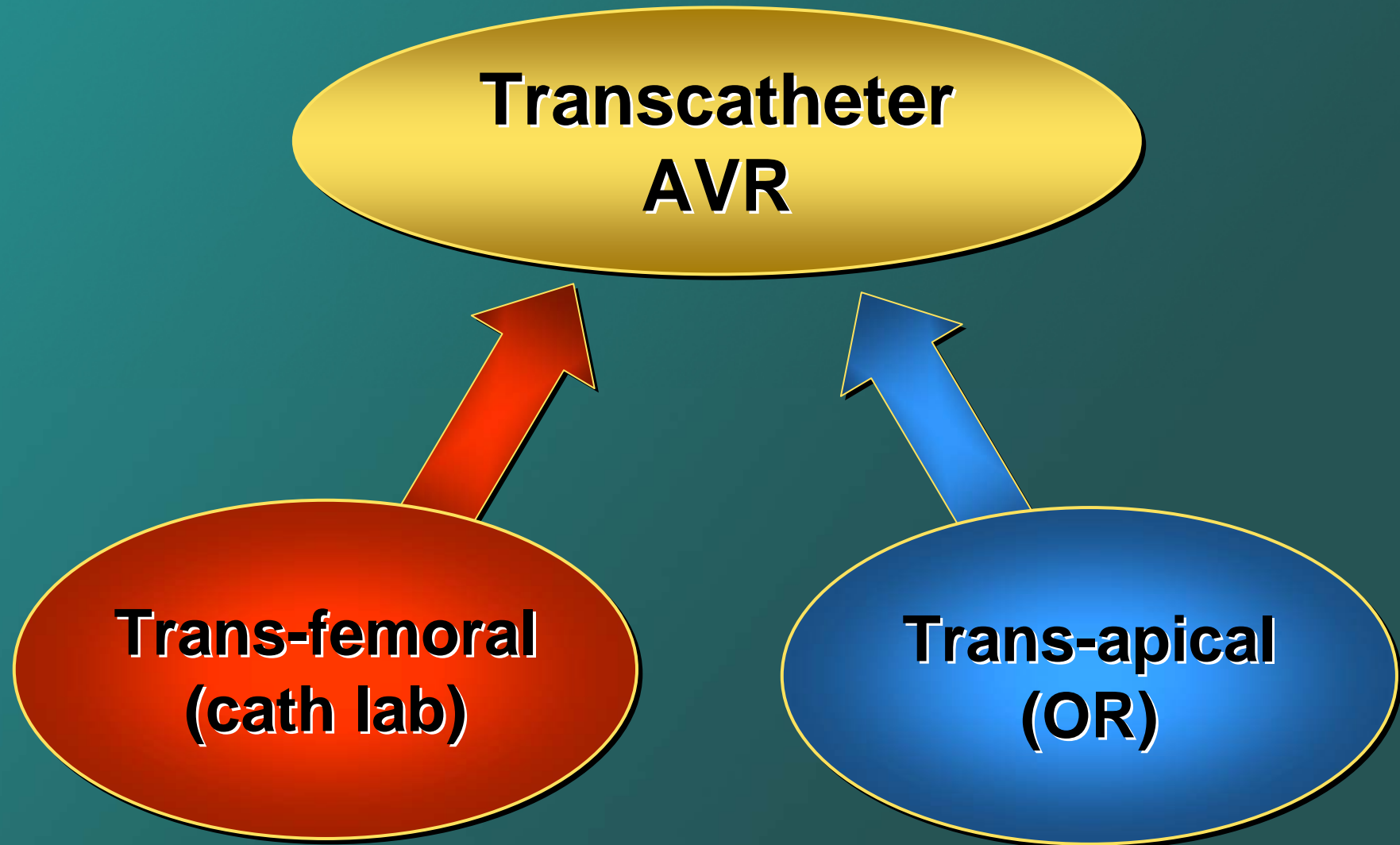
Transcatheter AVR

Antegrade Transeptal Approach

- **Transeptal catheterization and septal dilatation with 10 mm balloon**
- **Trauma to the mitral valve with the stiff guidewire causing acute MR**
- **Small/hypertrophied LVs difficult to maneuver PHV**
- **Technically very challenging in high risk patients**



Transcatheter AVR Technologies



Transcatheter AVR Technologies

**Catheter-Based
AVR**

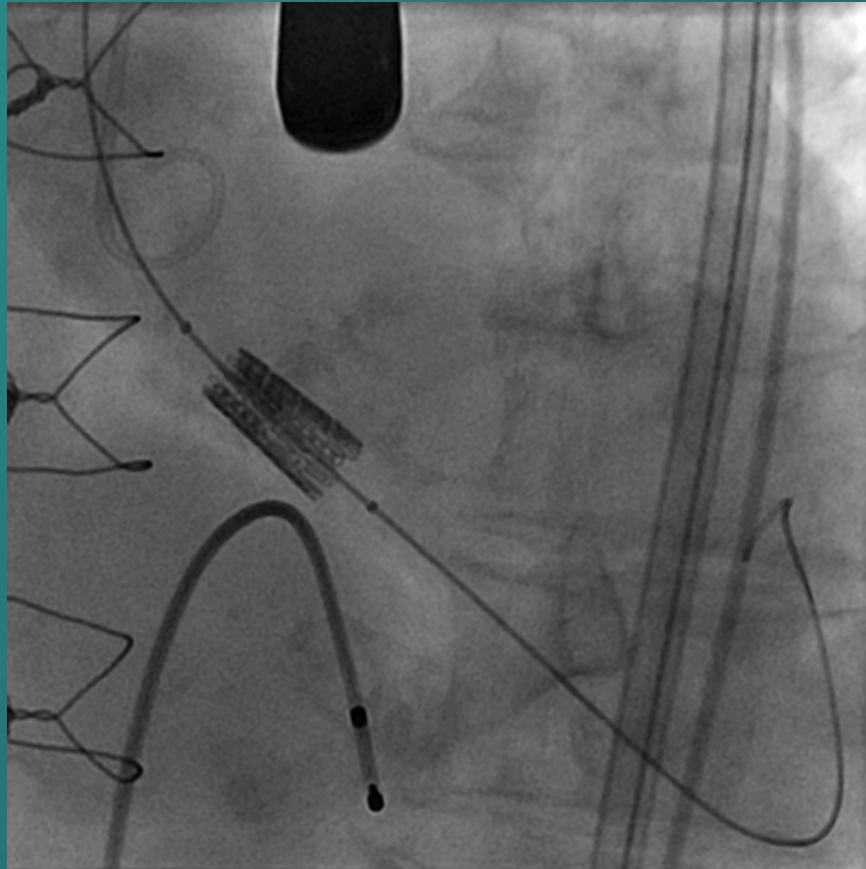
Preferred

**Trans-femoral
(cath lab)**

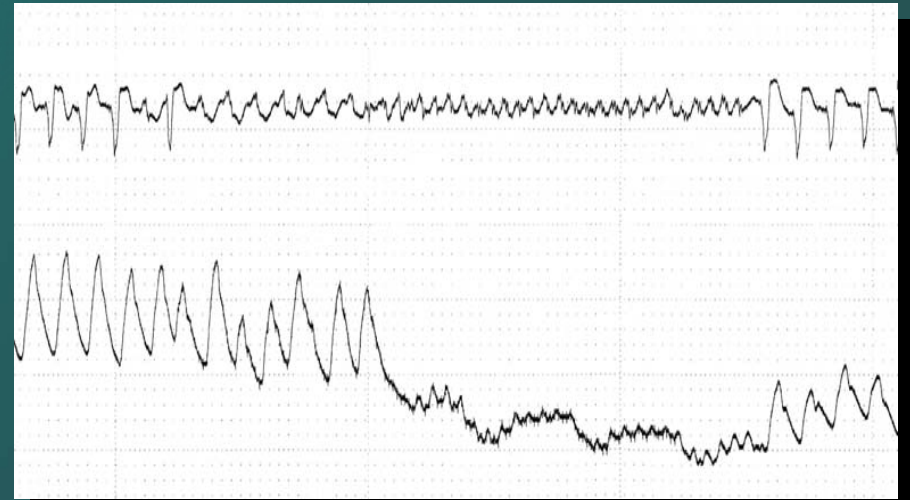
- Good vascular access
- No Ao arch pathology
- Retrograde AV crossing predictable



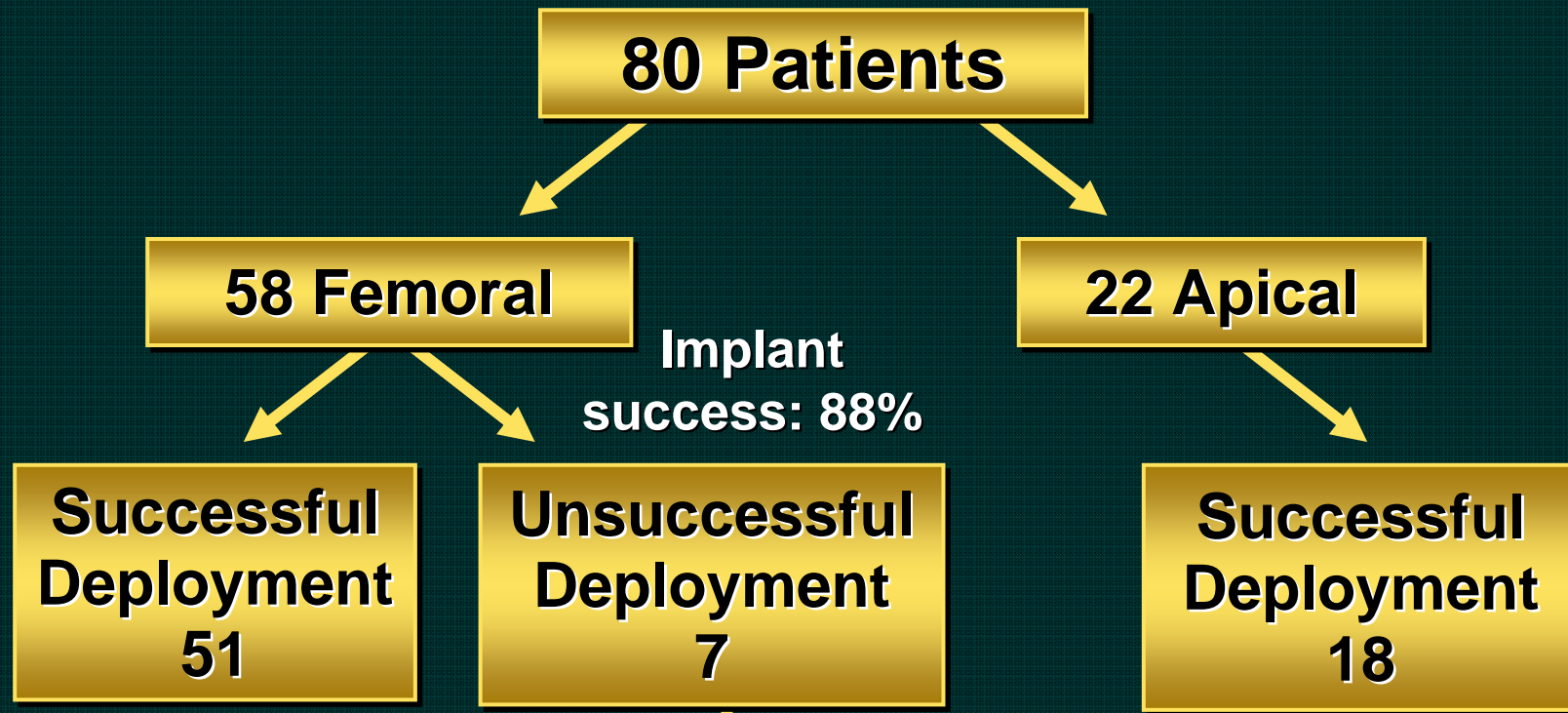
Retrograde Trans-femoral Deployment



Rapid pacing : 220/min

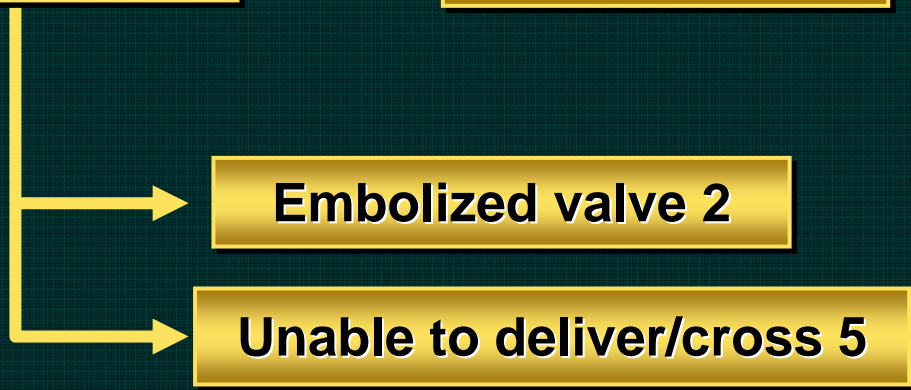


St. Paul's Hospital Vancouver Experience



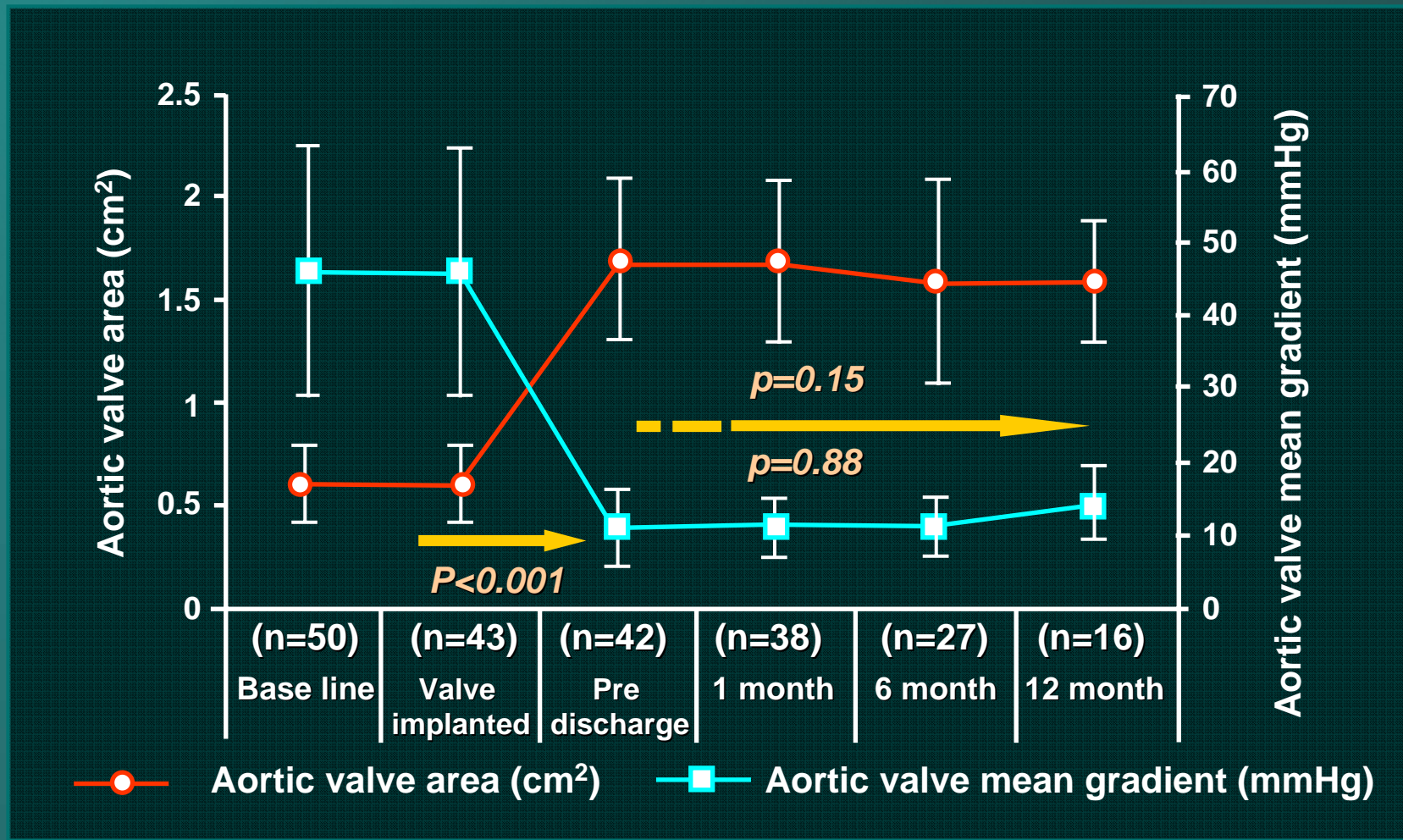
30-day mortality: 12.1%
30-day stroke: 3.4%
Logistic EuroSCORE: 28%

J. Webb and colleagues



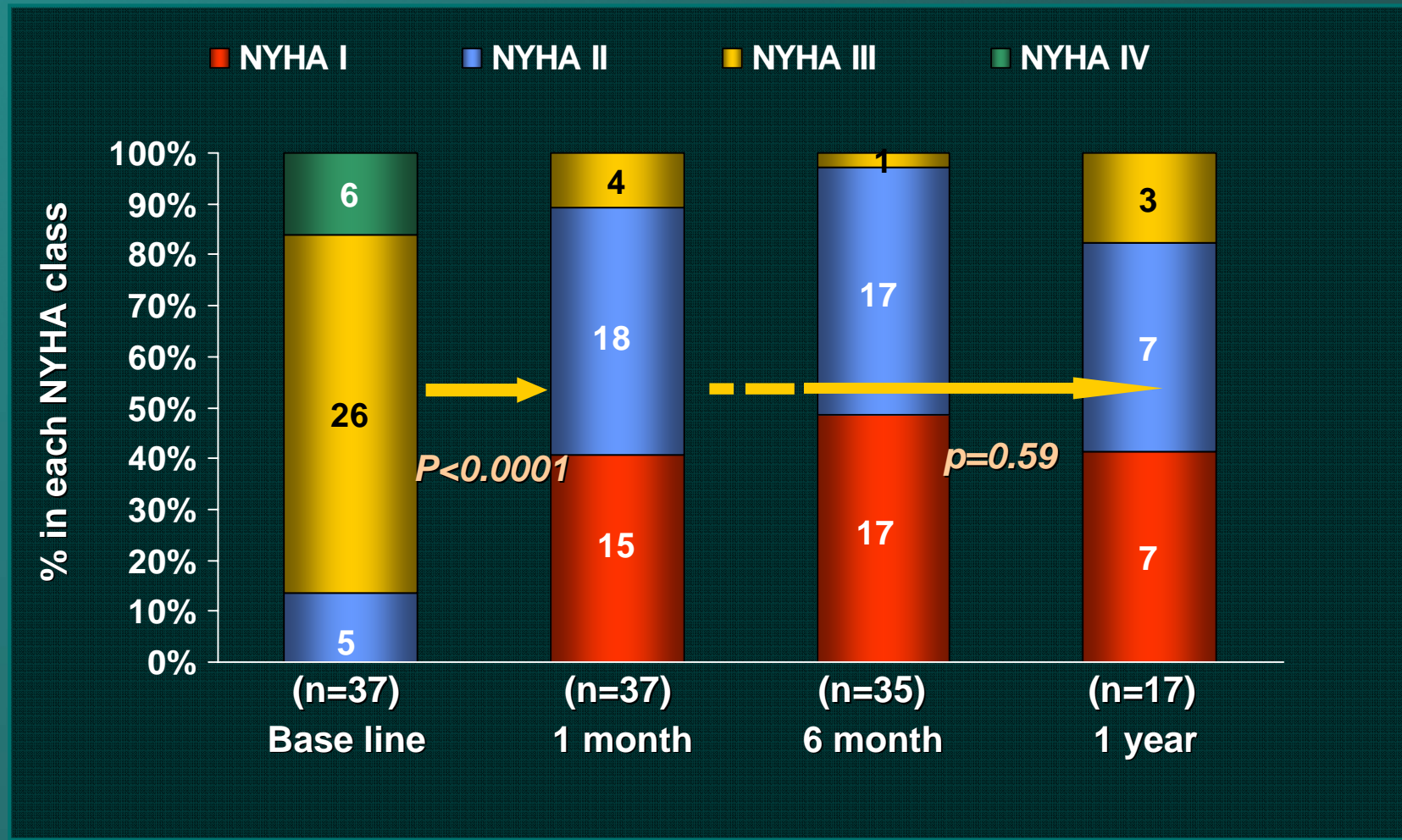
tAVR: Vancouver Experiences

AV Area and Gradients



tAVR: Vancouver Experiences

Symptom Status



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*

Centers:

29 Columbia
15 Beaumont
11 Cleveland
Clinic

PI: Wm O'Neill

**Trans-femoral
55**

**Successful
Deployment
48**

**Unsuccessful
Deployment
7**

**Implant
success: 87%**

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

Failed access 3

Malpositioned valve 1

Unable to cross 3

*** Updated April, 2007**

REVIVAL II – Clinical Outcomes

	In-Hospital	< 30 Day	6 Months *
MACCE	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
Other			
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%)**

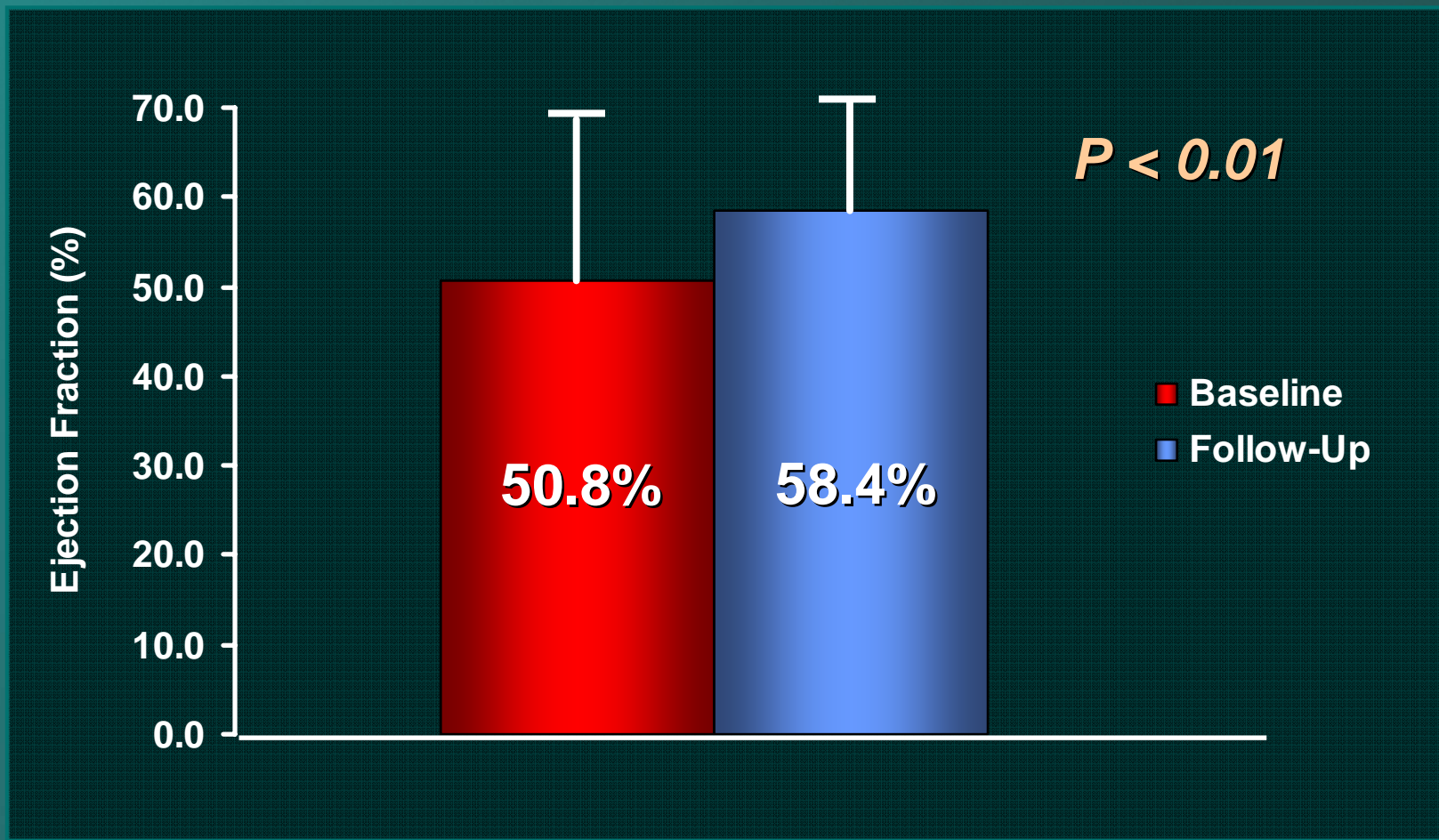
* Two patients have not reached six month time point yet

** One patient on CVVHD prior to valve implantation



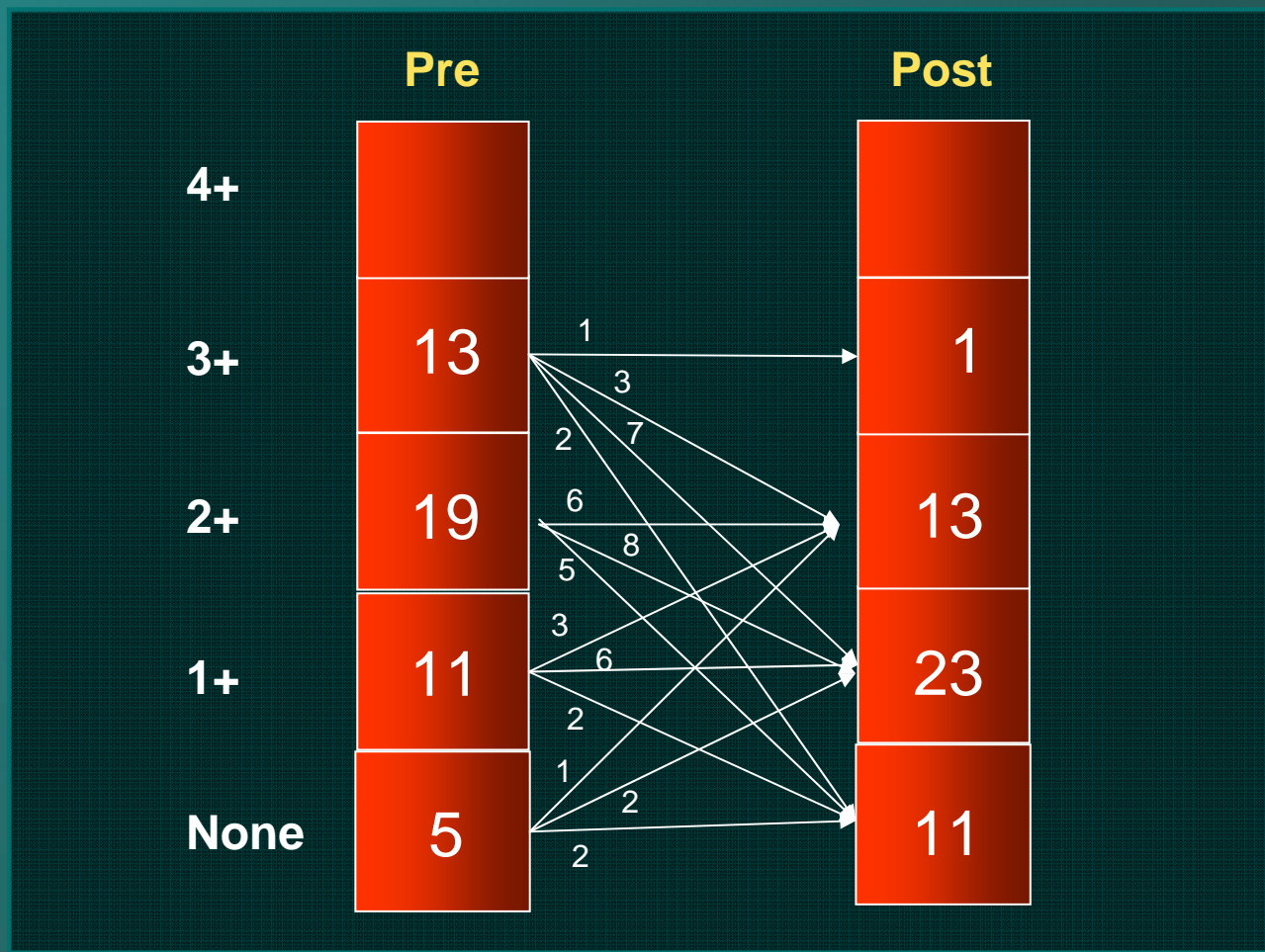
REVIVAL II

LVEF Following Valve Implantation



REVIVAL II

Aortic Regurgitation Post Procedure (n=48)



Transcatheter AVR Technologies

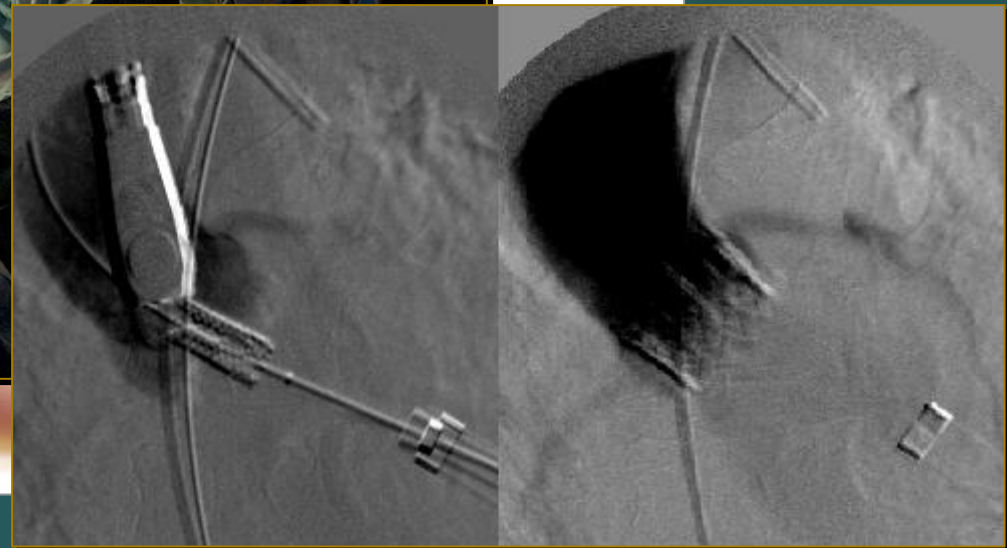
**Transcatheter
AVR**

Preferred

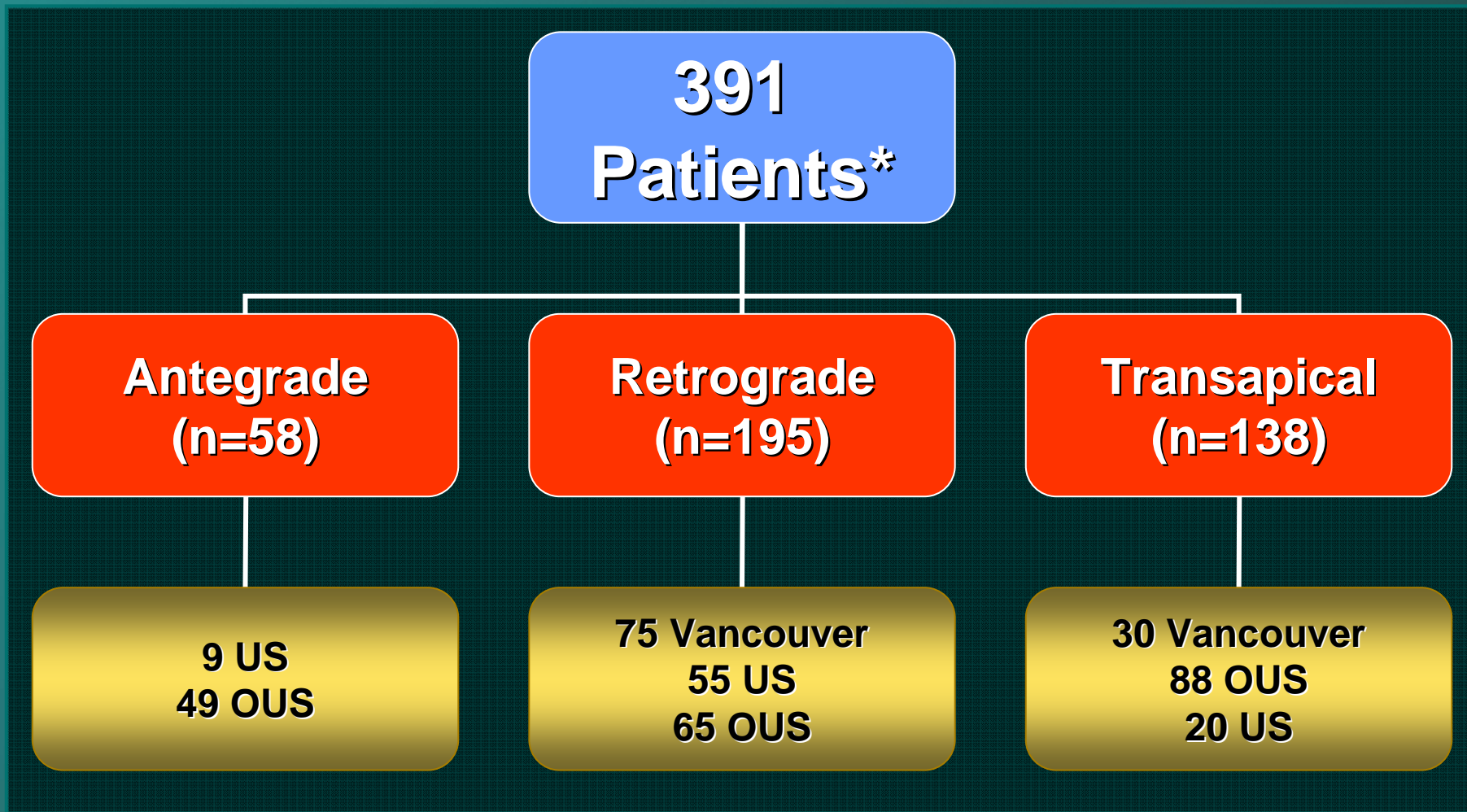
- **Poor vascular access**
- **Ao arch pathology (bulky atheroma or porcelain Ao)**
- **Retrograde AV crossing difficulties**

**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

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

High Risk Symptomatic Critical Aortic Stenosis

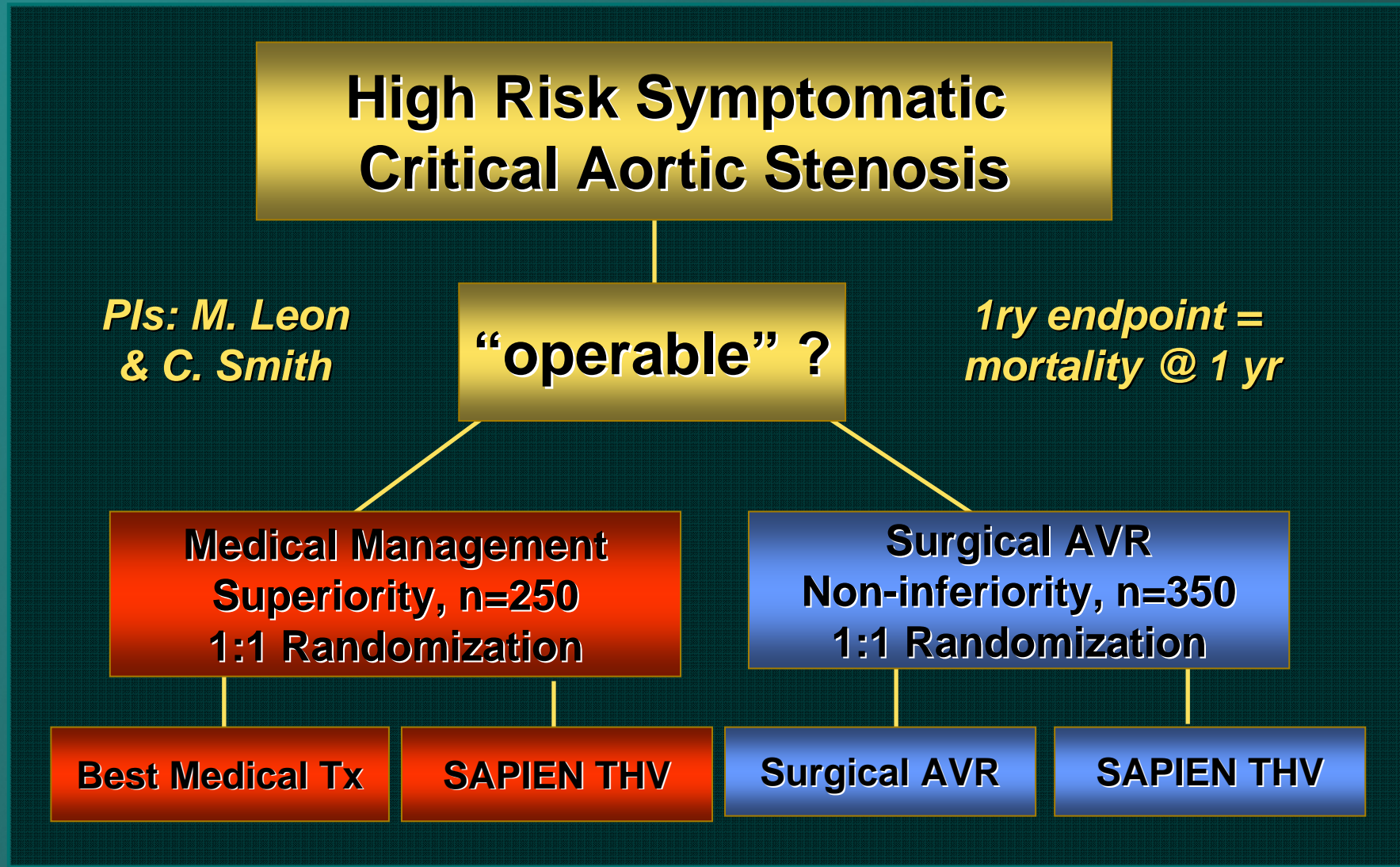
Eligibility

Transfemoral

Transapical

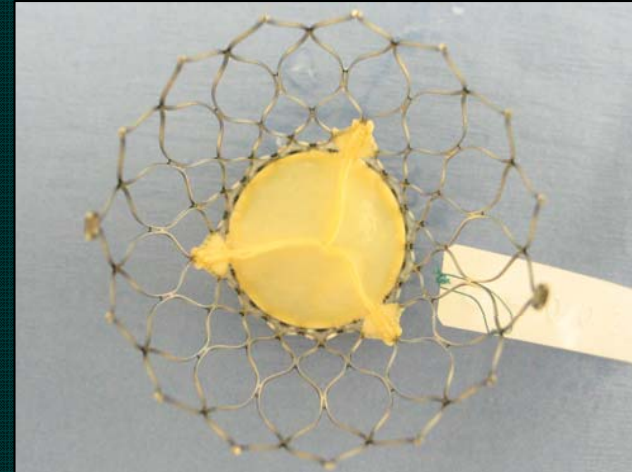


PARTNER US, Randomized Trials Total = 600 Patients



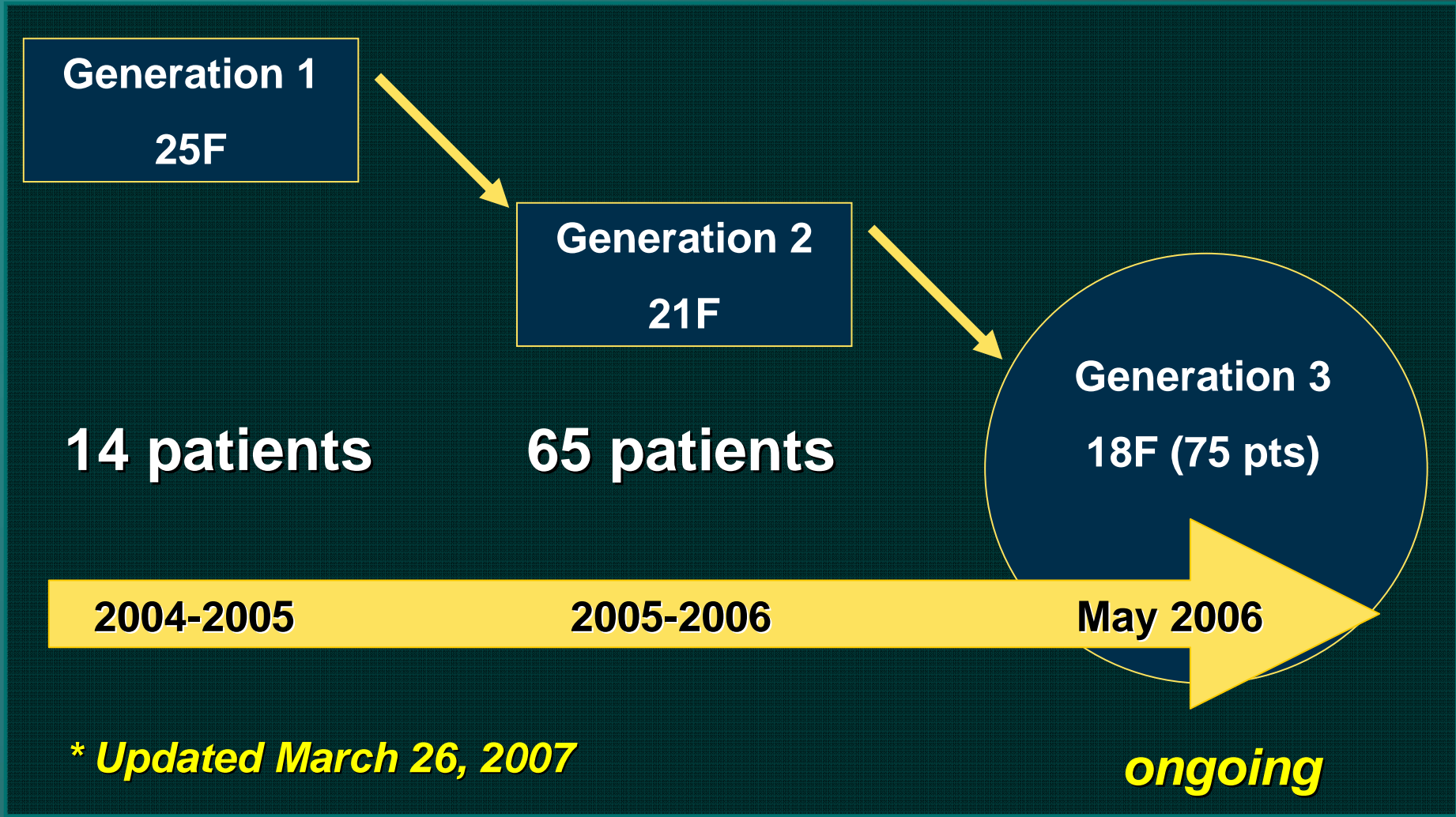
tAVR: CoreValve

- 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

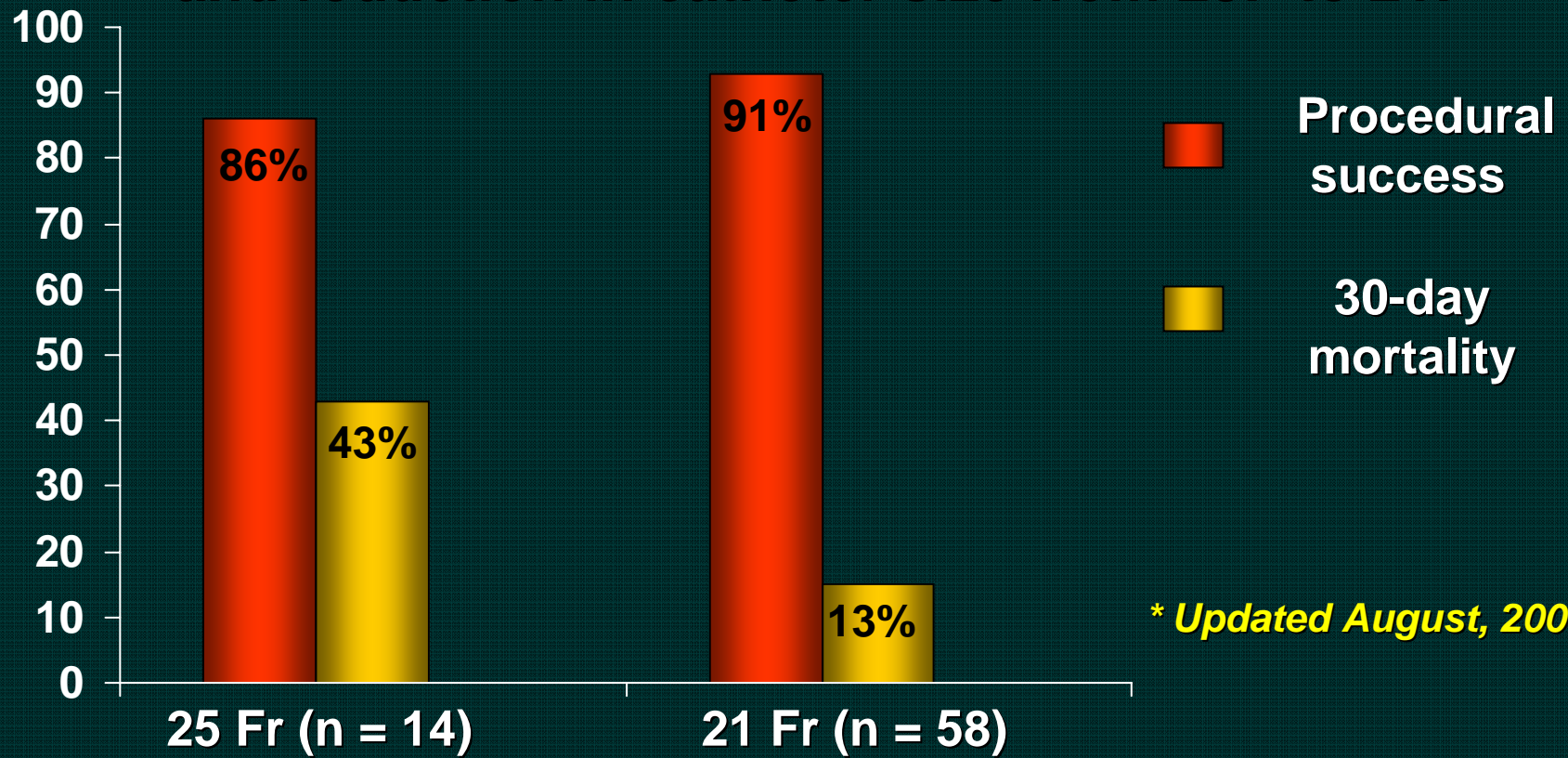
*Clinical Experience: 154 Patients**



CoreValve Self-Expanding Bioprosthesis

*Clinical Experience: 72 Patients**

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



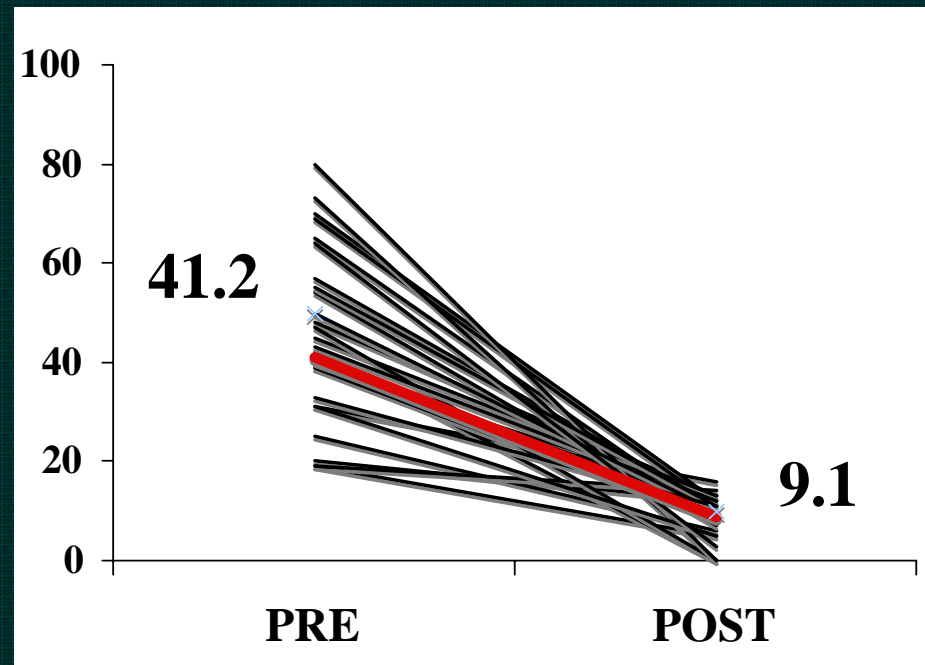
CoreValve 21F Experience

Post-procedure Result (TEE)

N=57

Mean gradient Post (mm Hg)
 9.1 ± 4.5 [0-19]

ASA (cm²)
 1.59 ± 0.40 [1.1-2.3]



CoreValve 21F Experience

Post-procedure Result (TEE)

N=57

Paravalvular leak

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

** Type A Aortic dissection*



CoreValve 21F Experience: *In-Hospital Major Complications*

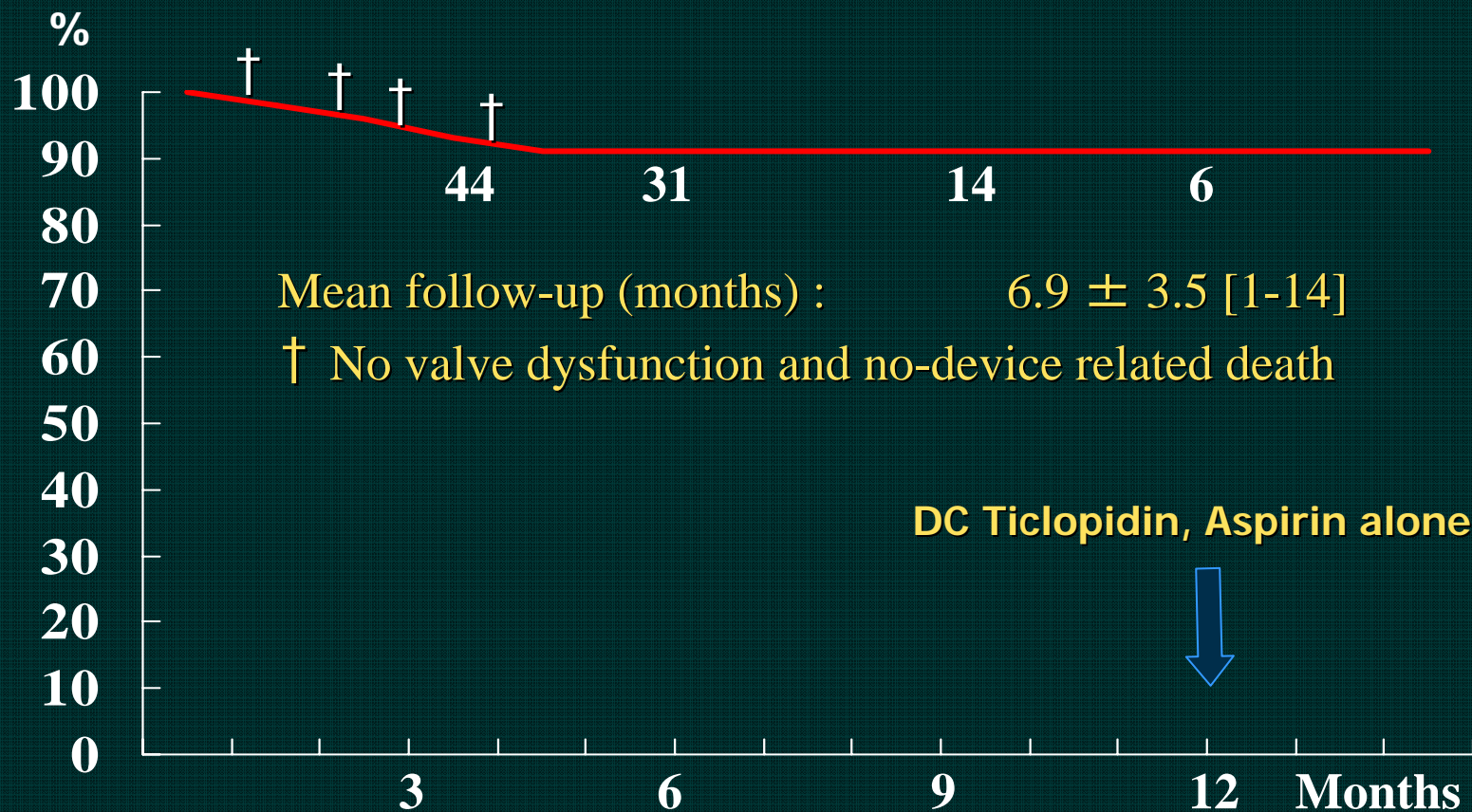
	High-Risk (N=50)	Inoperable (N=13)	Overall (N=63)
logistic EUROSCORE	23.4%	31.6%	25.4%
In-hospital mortality	8.0% (4)	30.8% (4)	12.7% (8)
Conversion to surgery	8.0% (4)*	-	6.4% (4)
Discharged and well	86% (43)	54% (7)**	80% (50)
Discharged inclusive of surgery & BAV only		87% (55)	

* High risk group: 1 converted patient died

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

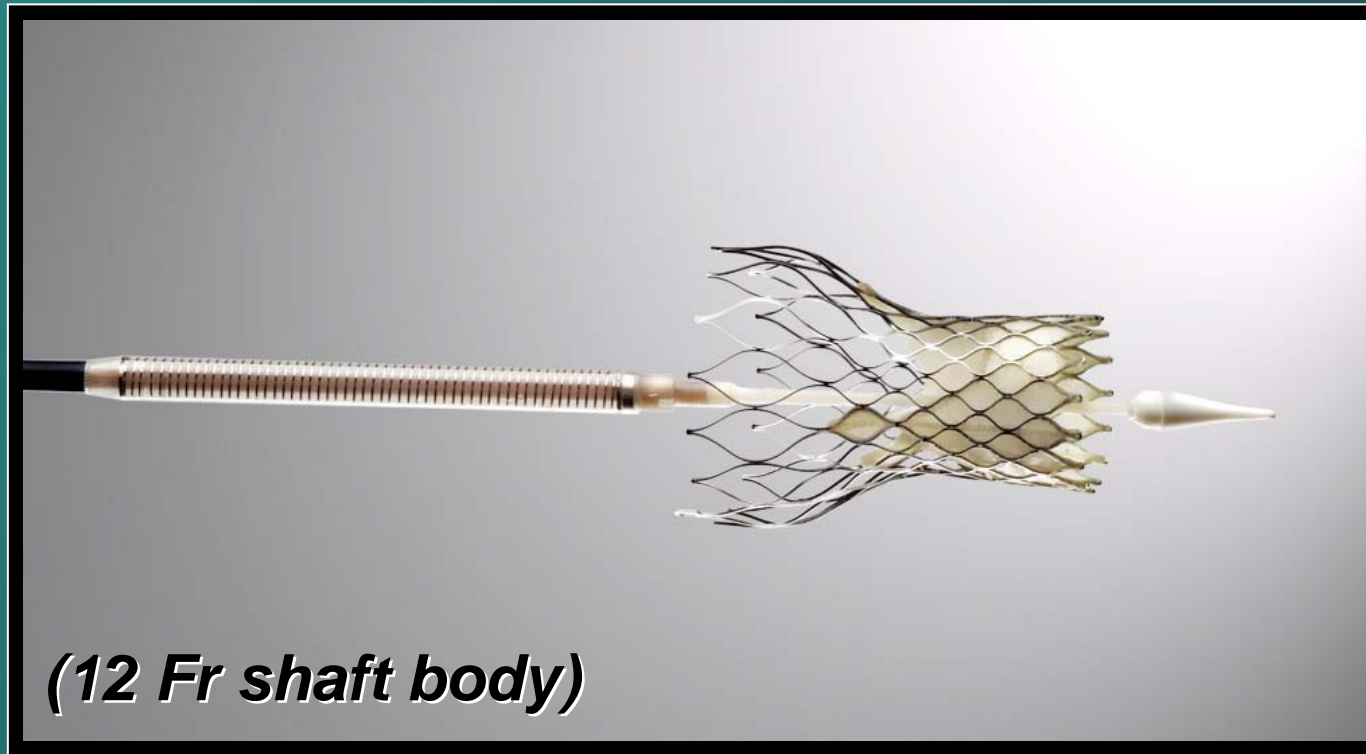
CoreValve 21F Experience

Lifetable Analysis (n=50)



CoreValve ReValving™ System

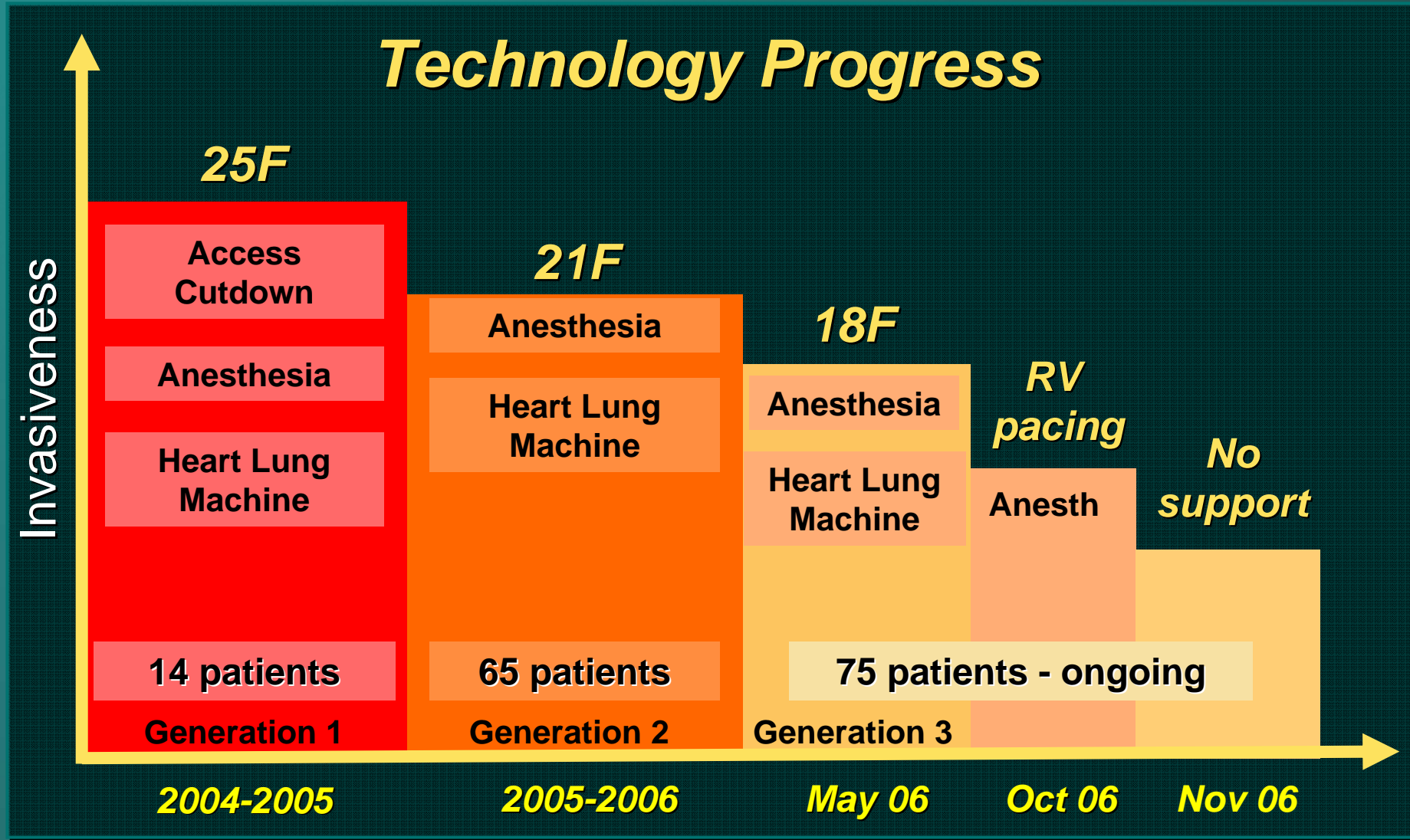
18 Fr Delivery System



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

30 Day Outcomes

	<i>Overall</i>	<i>21 Fr</i>	<i>18 Fr</i>
<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**



Transcatheter AVR

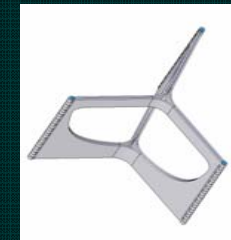
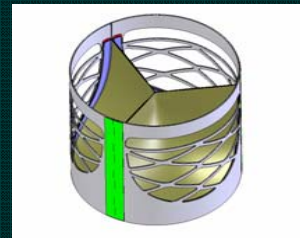
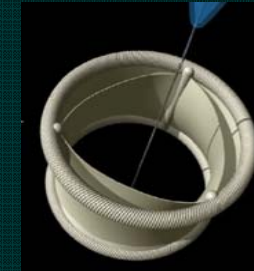
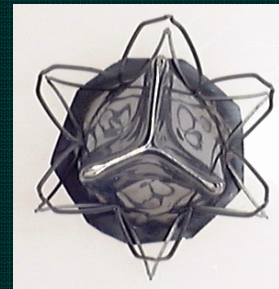
The Future and Conclusions...



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



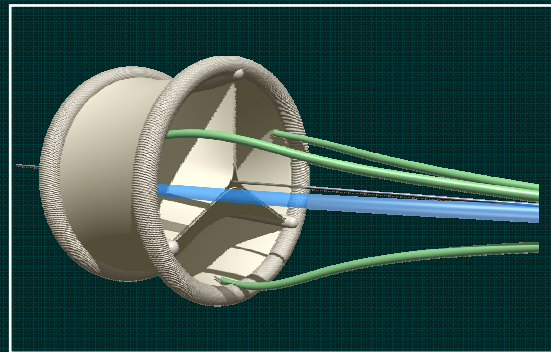
Transcatheter Valve Therapy

Next Generation Devices

Lower profile, repositionable, less pAR



AorTx



DirectFlow



Sadra



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**

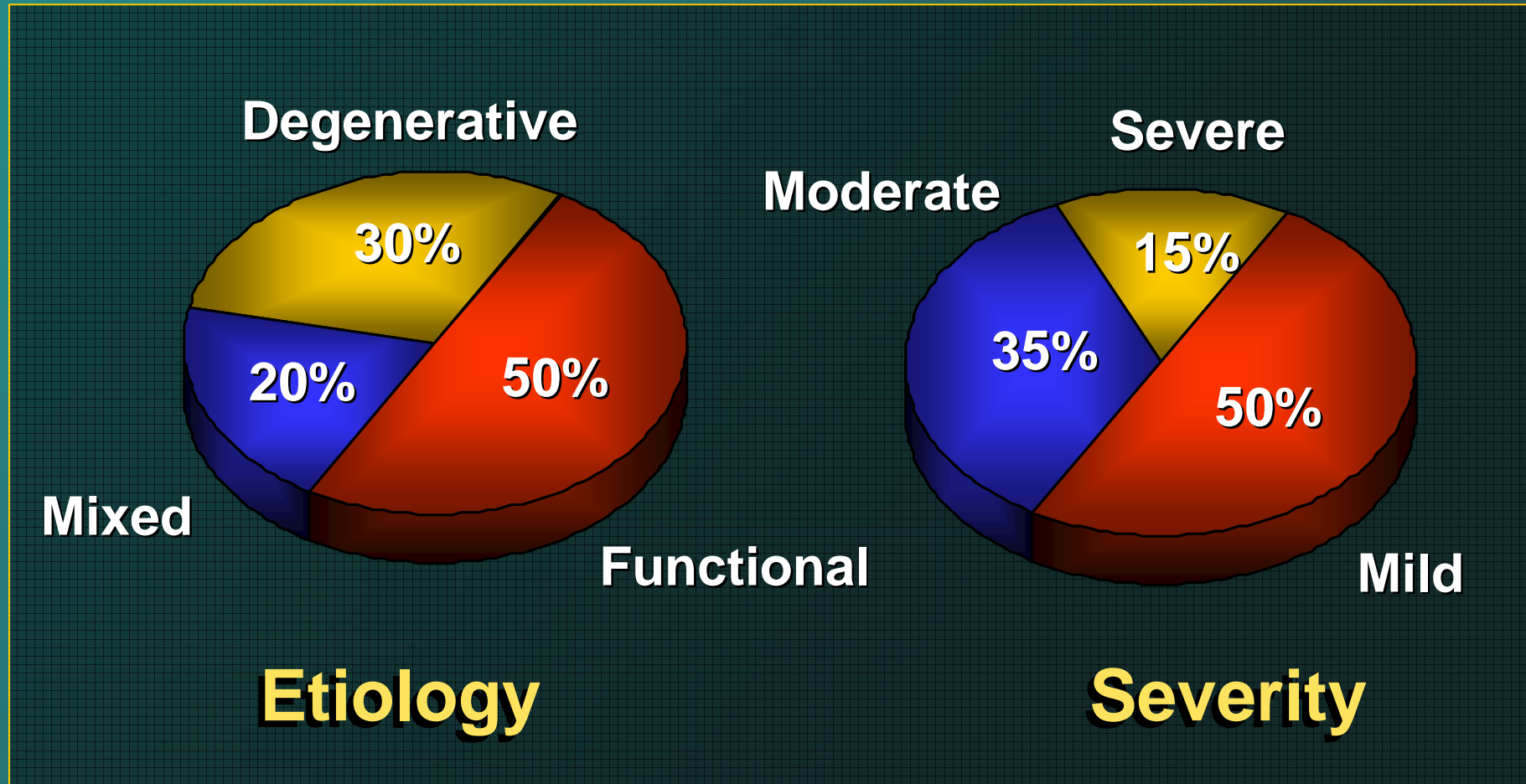


Transcatheter Valve Therapy

- ***For stenotic valves***
 - Pulmonary (or valve conduit) stenosis (a/o regurgitation)
 - Aortic stenosis
 - Mitral stenosis
- ***For regurgitant valves***
 - Aortic regurgitation
 - ***Mitral regurgitation***



MR Demographics: Disease Etiology and Severity



Edge-to-edge

- eValve
- Edwards Mobius

Coronary sinus annuloplasty

- Cardiac Dimensions
- Edwards Monarc
- Viacor

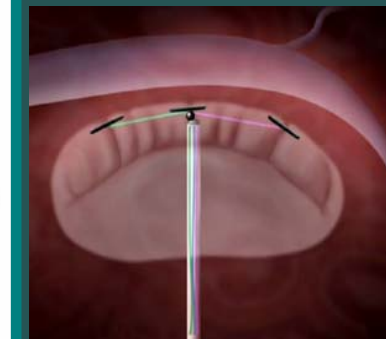
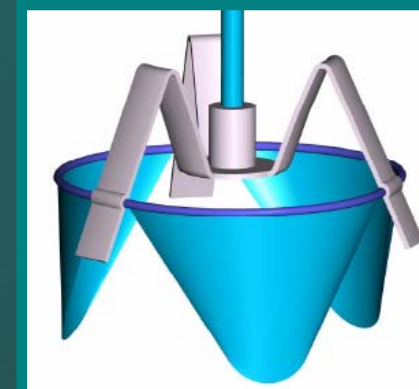
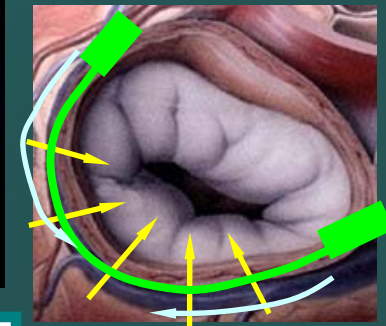
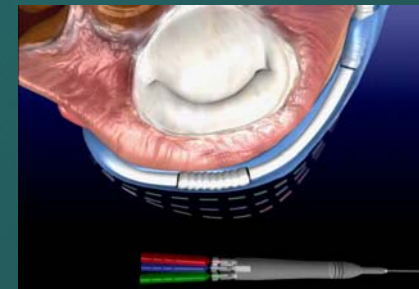
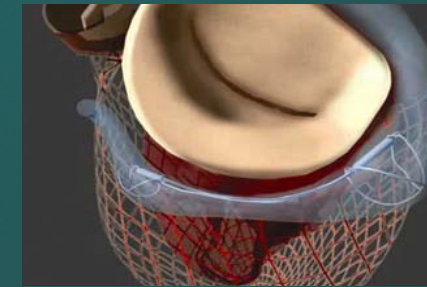
Indirect annuloplasty

- Ample PS3
- St. Jude
- i-Coapsys

Direct annuloplasty

- Mitralign
- Guided Delivery Systems
- QuantumCor
- MiCardia

Percutaneous MV Repair



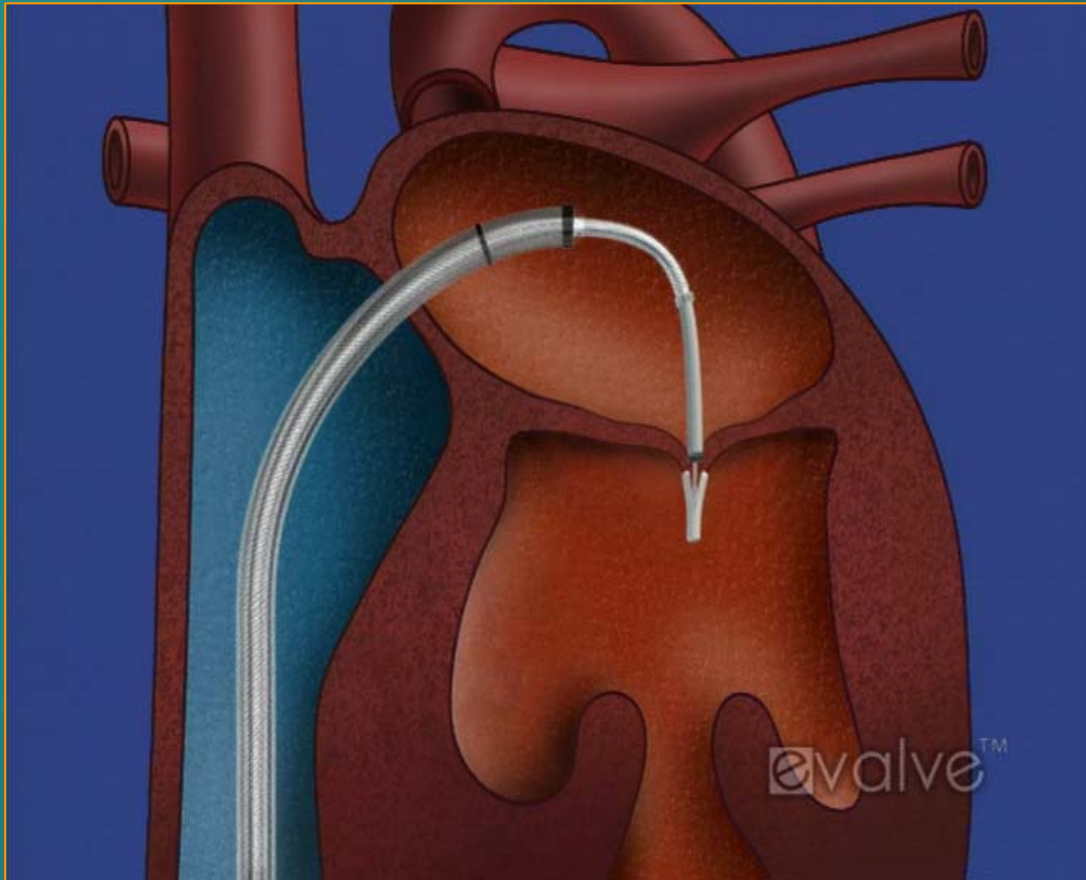
Percutaneous Treatment of Mitral Regurgitation

Edge-to-Edge Approaches

- Permanent leaflet-to-leaflet approximation using a clip or sutures + clip
- Trans-septal approach
- Echocardiographic and fluoroscopy guidance on a beating heart
- **Companies**
 - Evalve
 - Edwards (Milano II = MOBIUS)



Sophisticated Delivery Systems (Evalue)



EVEREST I & II Registry Enrollment with 30 day Core Lab Follow-Up

Study	Population	n
EVEREST I (Feasibility)	All patients enrolled	55
EVEREST II (Pivotal)	Non-randomized patients (Excluding High Risk Registry)	49
Total		104

- **29 North American sites**
- **72% are 1st, 2nd, or 3rd procedure at a site**



EVEREST I & II

Key Eligibility Criteria

- Age 18 years or older
- Moderate to severe (3+) or severe (4+) MR
 - *Symptomatic*
 - *Asymptomatic with LVEF <60% or LVESD >45mm*
ACC/AHA Task Force Guidelines JACC 1998;32:1486
- MR originates from A2-P2 mal-coaptation
- Core lab echo assessment
ASE Guideline - JASE 2003;16:777-802
- Candidate for mitral valve surgery including CPB
- Transseptal deemed feasible
- Key Exclusions
 - *EF < 25% or LVESD > 55 mm*
 - *Renal insufficiency*
 - *Endocarditis, rheumatic heart disease*



EVEREST I & II Registry

MR Etiology (104 pts)

Degenerative/Mixed **81 (78%)**

Posterior Prolapse/Flail 56 (69%)

Anterior/Bi-leaflet 25 (31%)

Prolapse/Flail

Functional **23 (22%)**



EVEREST I & II Registry

30 Day MACE (104 pts)

Freedom from Major Adverse Cardiac Events

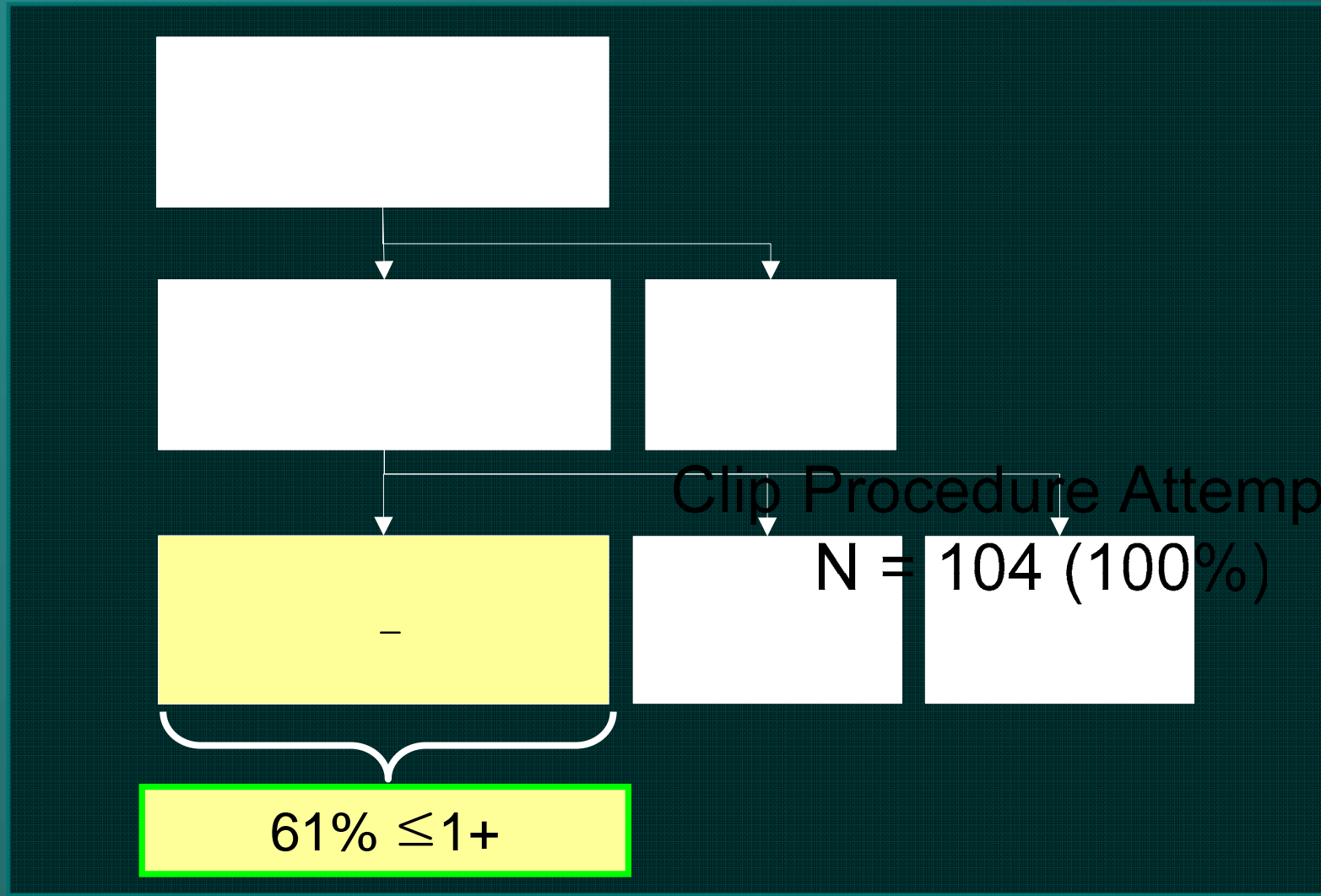
94%

Death – Unrelated to Clip	1
Stroke (>72 hours)	1
Renal failure	0
Non-elective Cardiac Surgery	1
Bleeding requiring transfusion	3
Myocardial Infarction	0
Septicemia	<u>0</u>
	6/104 (6%)



EVEREST I & II Registry

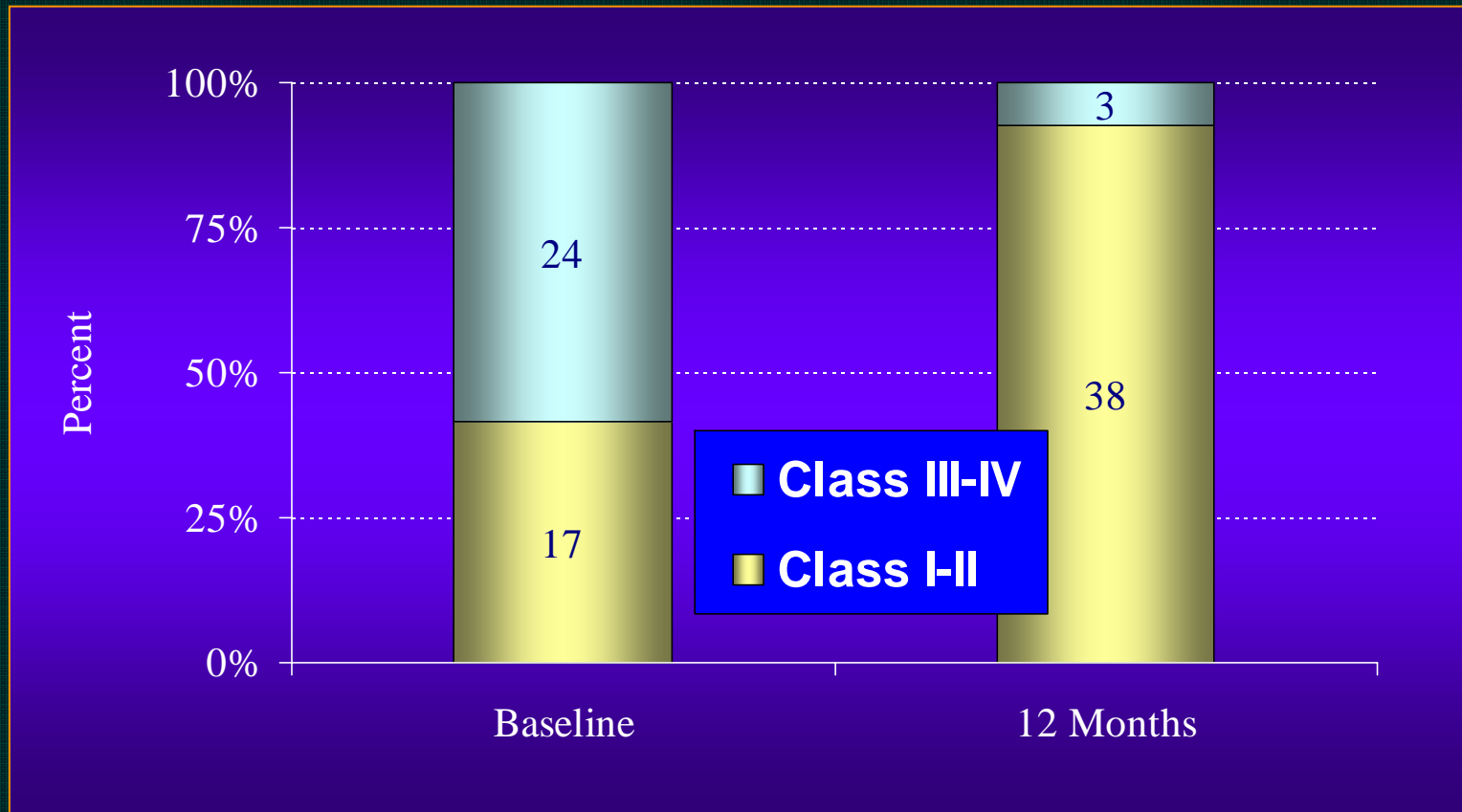
Procedural Results (104 pts)



EVEREST I & II Registry

Clinical Improvement after Procedural Success 12-Months vs. Baseline (Matched Data)

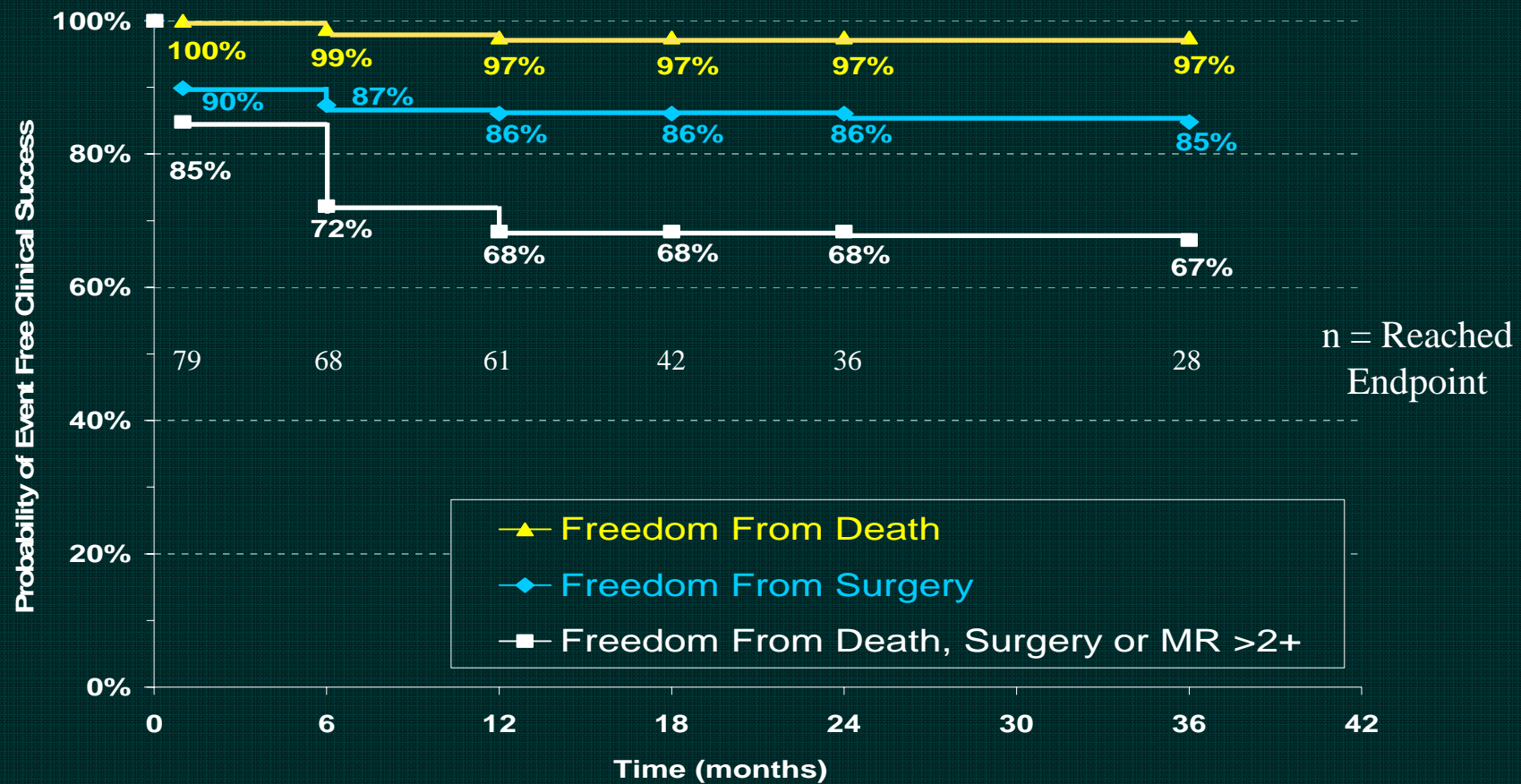
73% (30/41) Improved
24% (10/41) No Change
3% (1/41) Worsened to Class II



EVEREST I & II Registry

Event Free Clinical Success

Patients with Acute Procedural Success (79 pts)



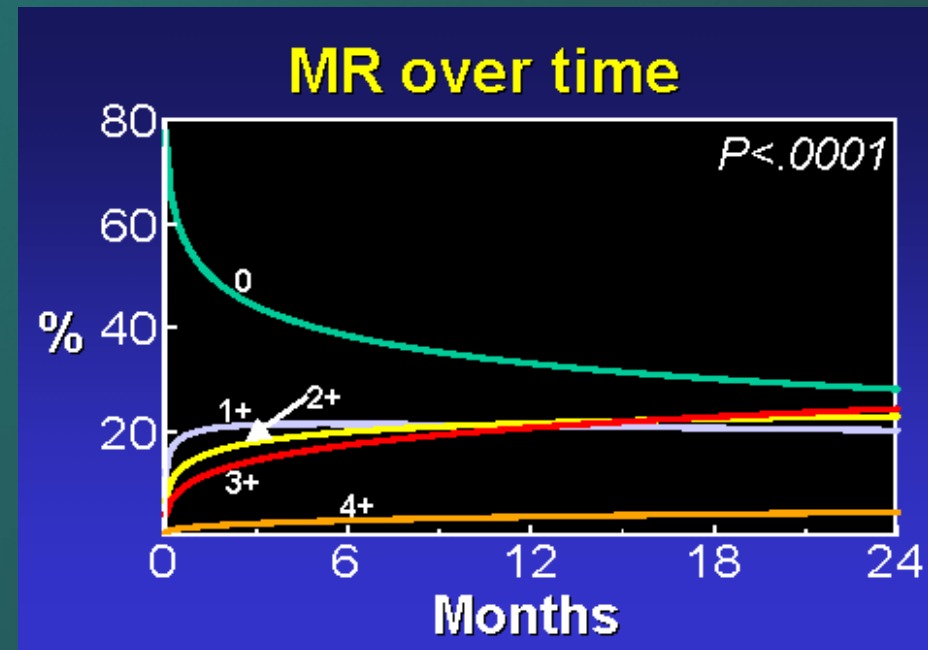
Freedom from death, mitral valve surgery, & MR>2

The Edge to Edge Approach to Mitral Regurgitation

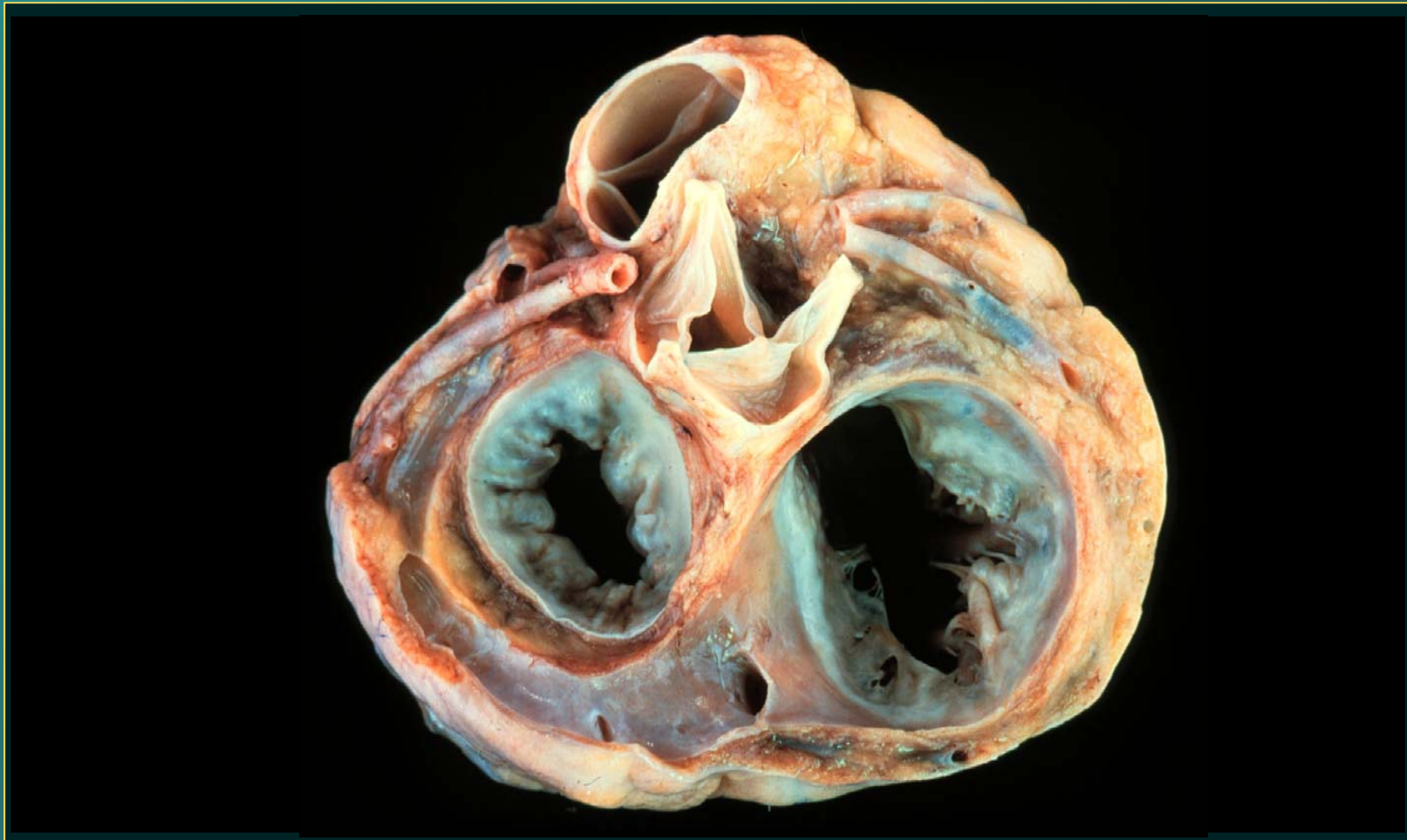
- **Potential issues**

- Technically complex
- Inclusion criteria may limit application
- Will it work without concomitant annuloplasty?
- Durability of repair?
- Endocarditis
- Leaflet degeneration and stress

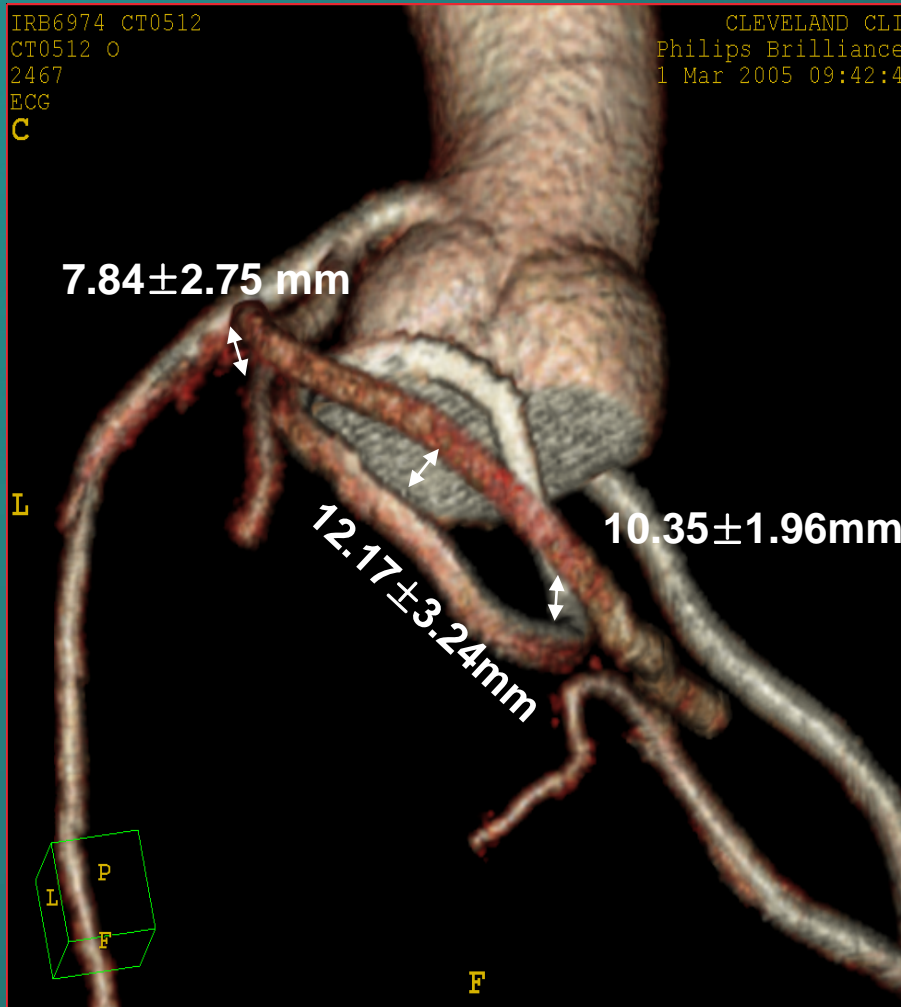
- **Might be used *with* annuloplasty devices**



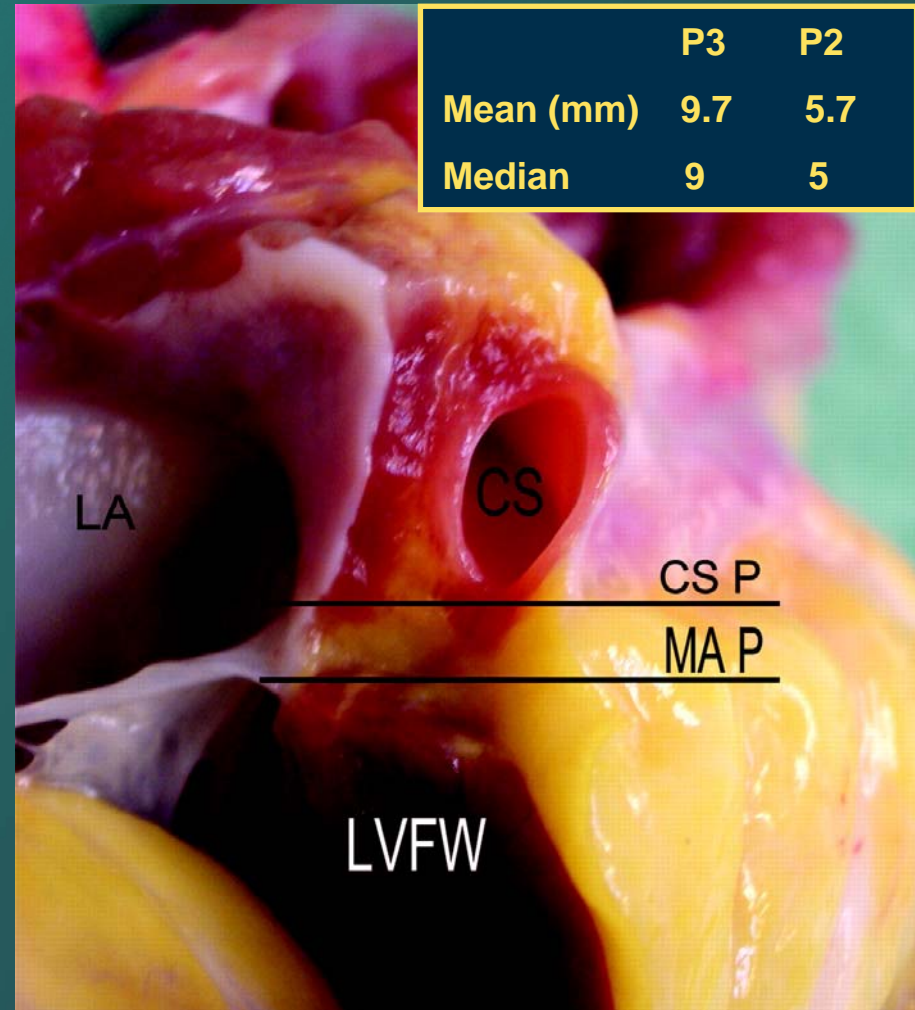
Percutaneous Treatment of Mitral Regurgitation



Indirect Annuloplasty: Issues and Problems - CS to MA Separation

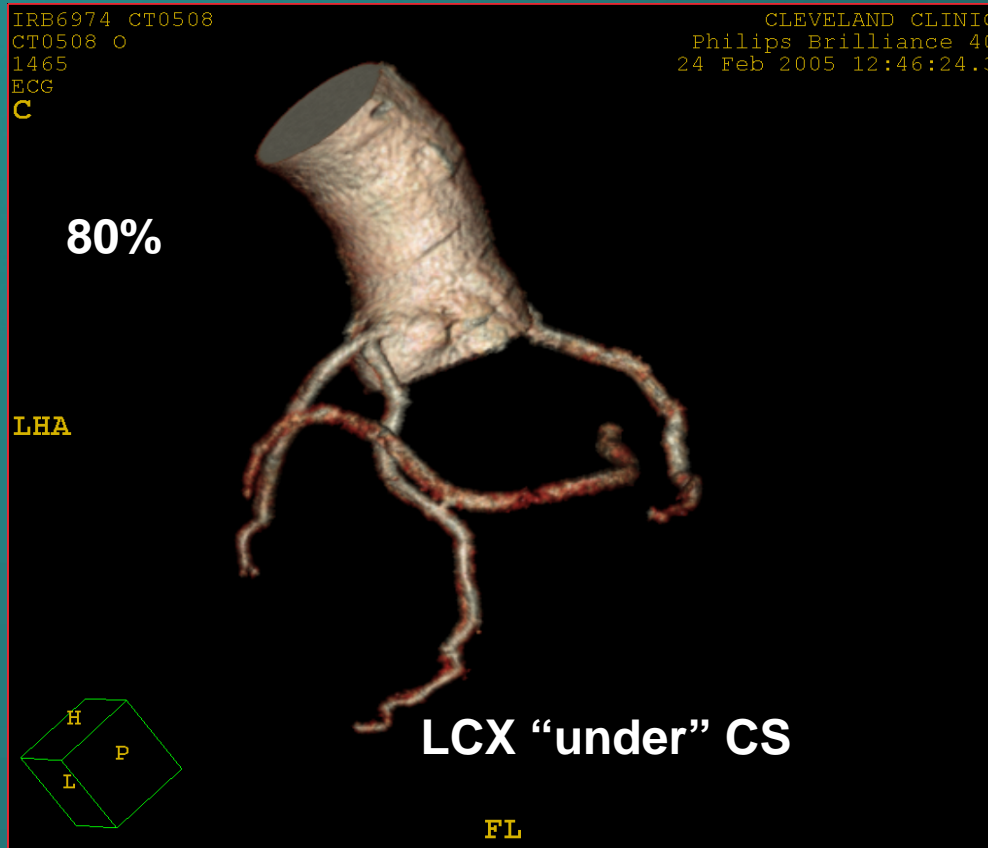


Courtesy Samir Kapadia, MD, Cleveland Clinic Foundation (JACC in press)



Maselli et al, *Circ* 2006;114:377-380

Indirect Annuloplasty: Issues and Problems - Relation of LCX and CS



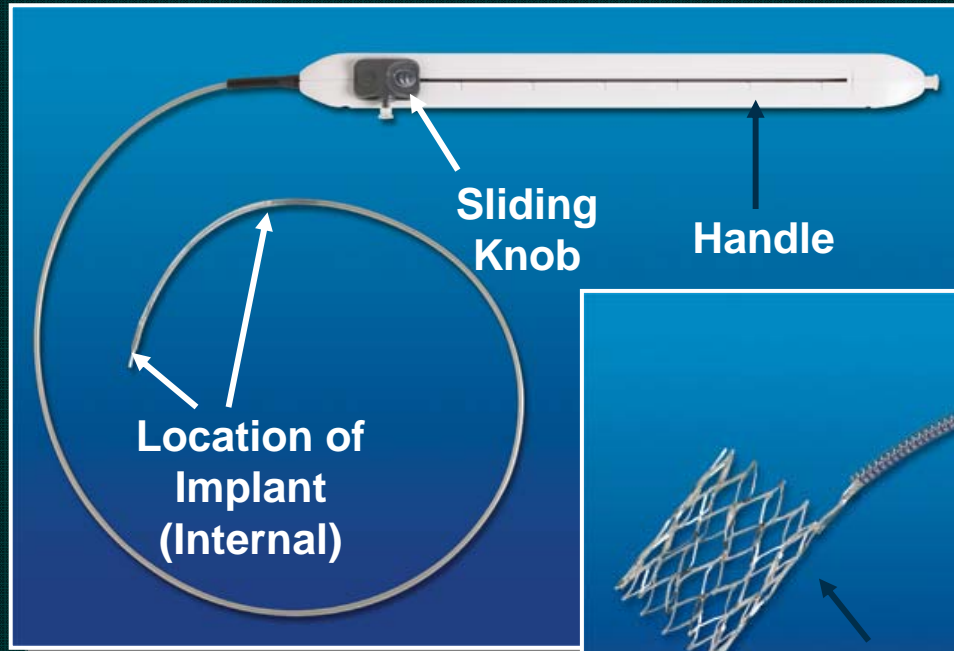
Maselli et al: *Circ* 2006;114:377-380

LCx crossed under 64%

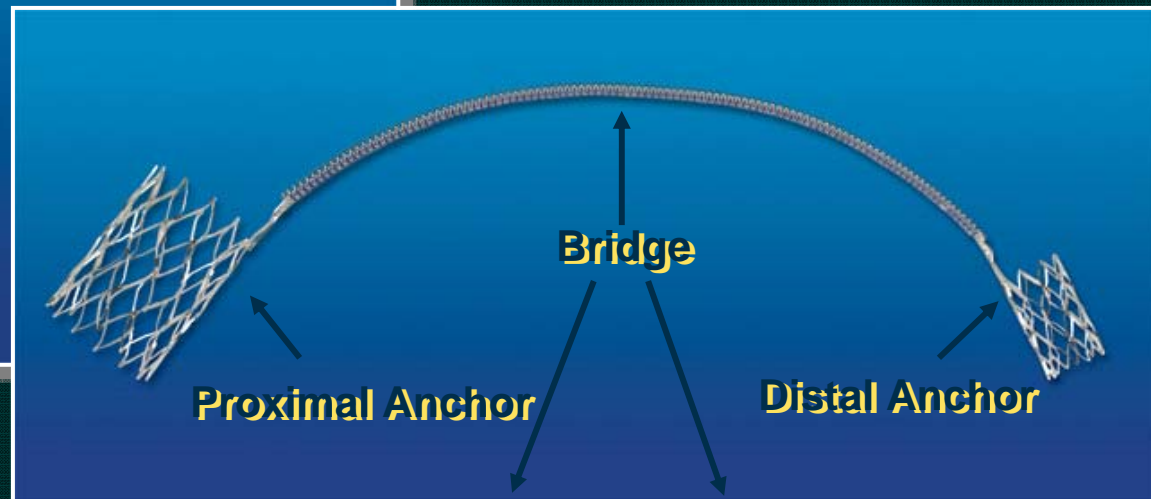
Diag / ramus 16%

Courtesy Samir Kapadia, MD, Cleveland Clinic

Edwards MONARC System

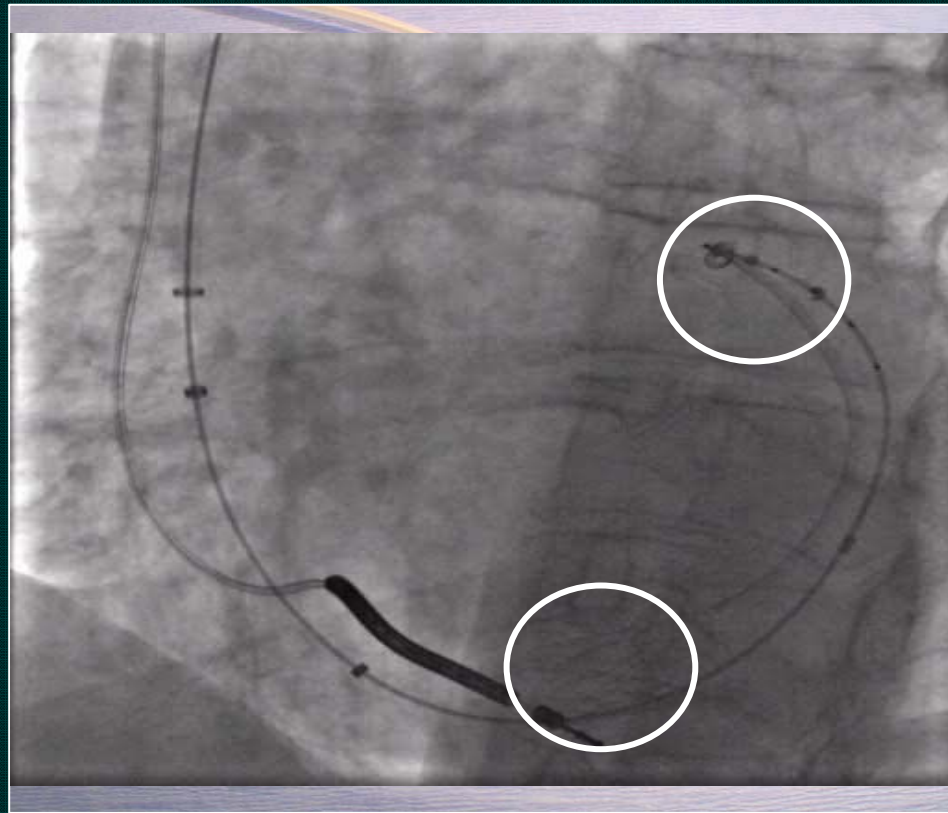


12F guiding catheter
9F delivery system

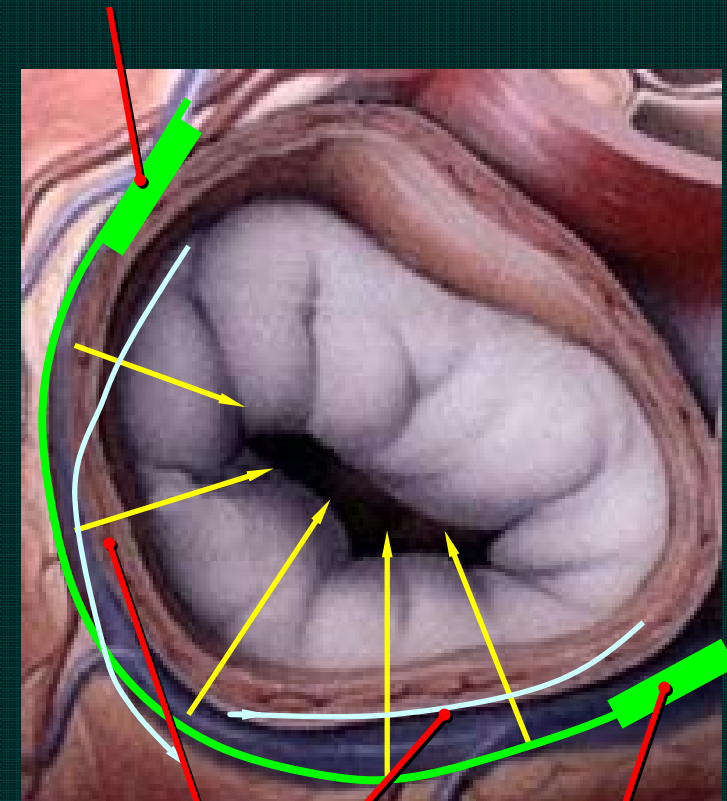


Edwards MONARC System

Foreshortening Implant



Distal Anchor



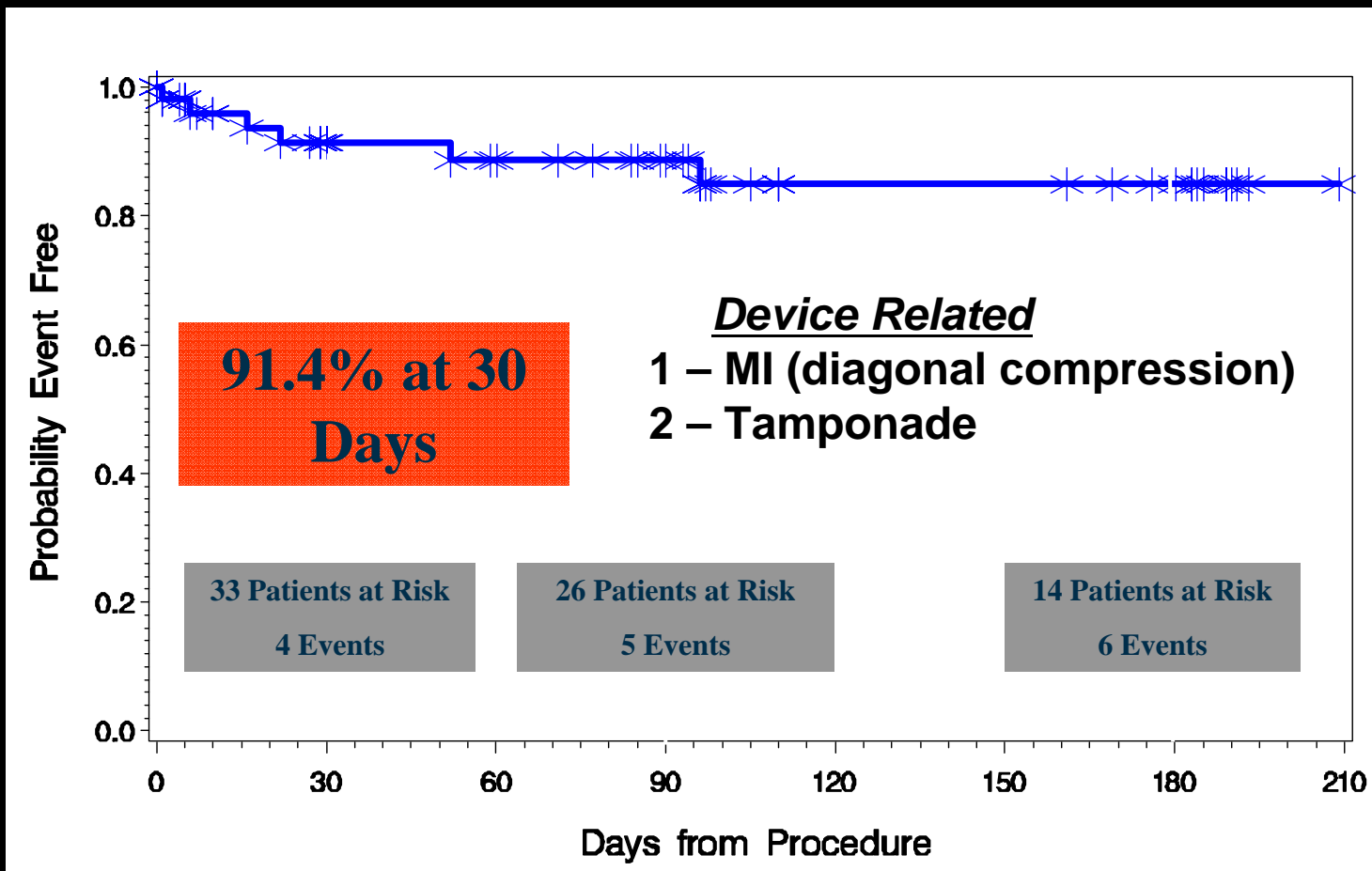
Foreshortening

Proximal Anchor

EVOLUTION (n=59 implants)

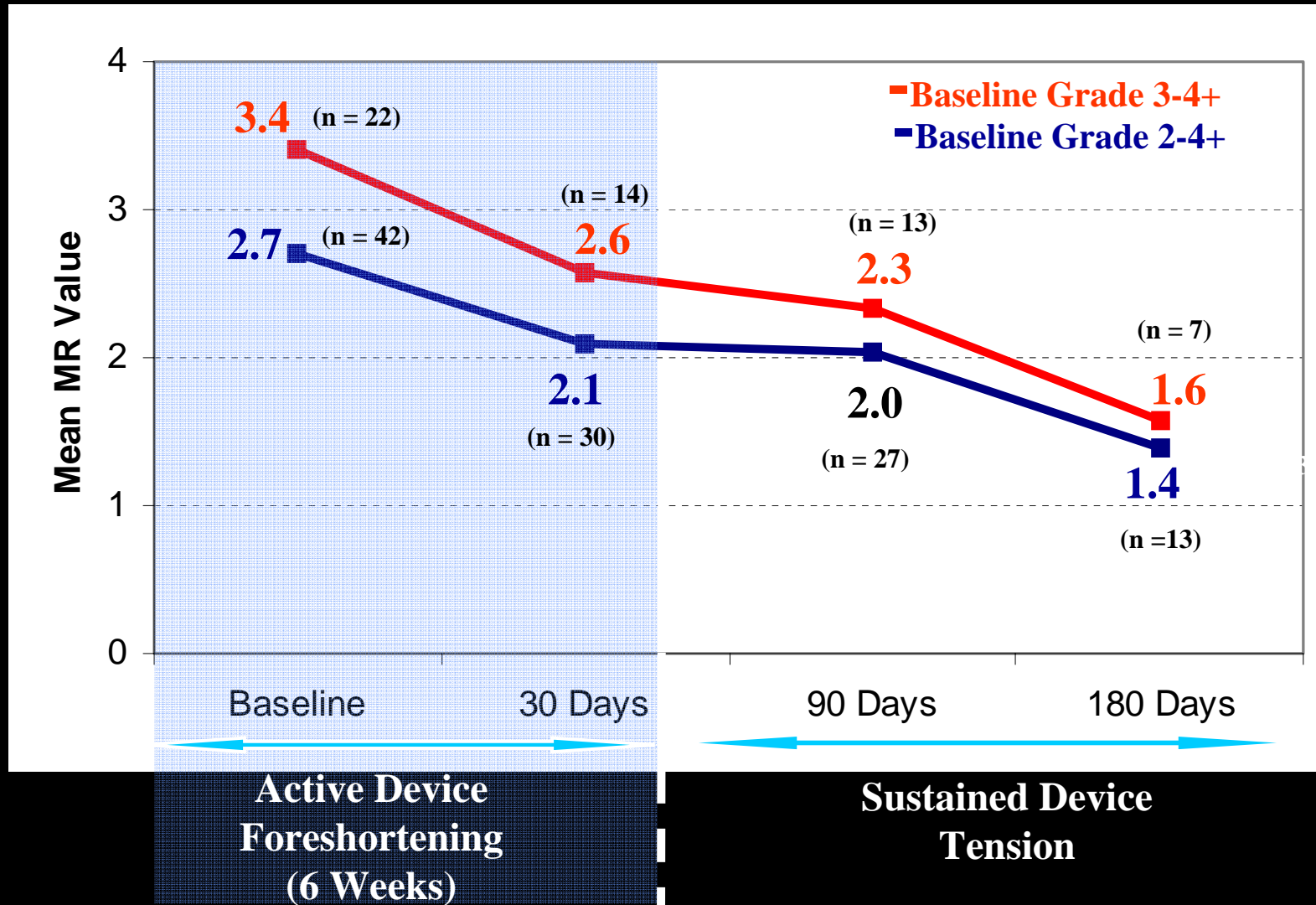
Safety endpoint analysis

Death, MI, or Cardiac Tamponade



EVOLUTION study

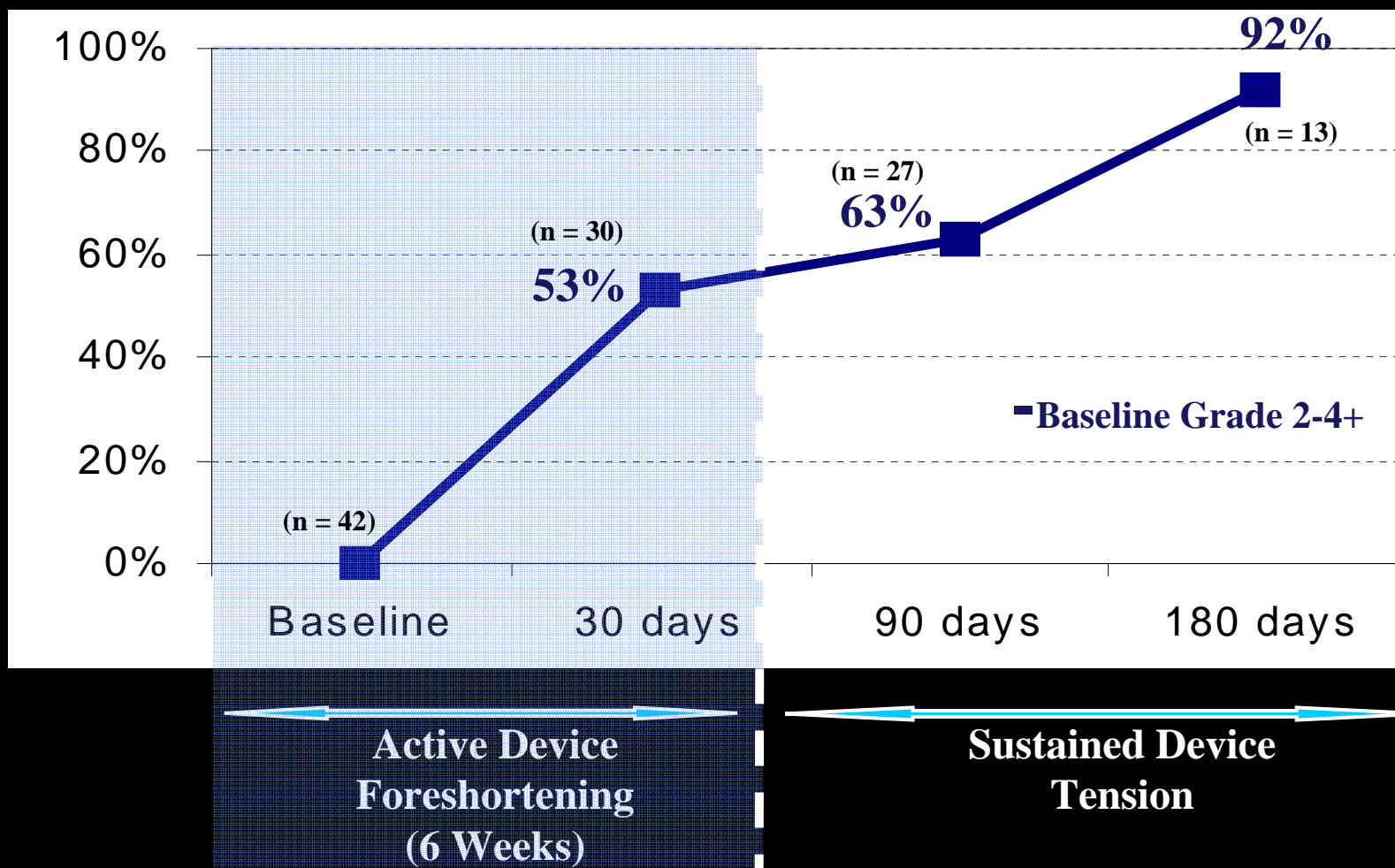
interim performance data



EVOLUTION study

interim performance data

% pts reduced MR \geq 1 grade



The Coronary Sinus Approach to Mitral Regurgitation

- **Potential problems**
 - ? Ability to reduce annulus in all patients
 - Relationship of CS to MV not perfect in ~20%
 - Mitral annular calcification?
 - Acute vs. sustained results?
 - Potential pinching of LCx artery
 - Risk of CS thrombosis/occlusion
 - Risk of CS erosion/perforation

If it works, this approach would be the simplest and most practical for many interventionalists

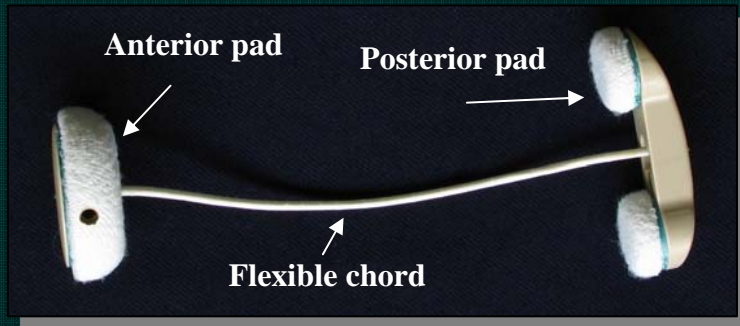
Percutaneous Treatment of Mitral Regurgitation

Indirect Annuloplasty Approaches

- Coronary sinus to RA or trans-ventricular approaches to reduce mitral annulus dimensions and correct ventricular remodeling (iCoapsys)
- Echocardiography and fluoroscopy guidance on a beating heart
- **Companies**
 - Ample PS3
 - St. Jude
 - iCoapsys

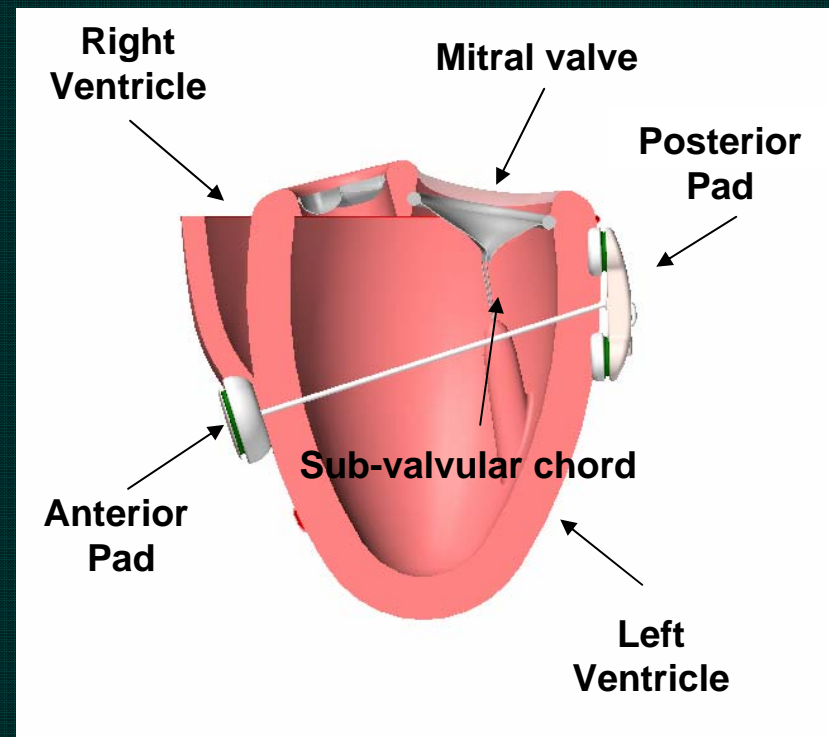


iCoapsys Implant & Therapy



- **Trans-pericardial access**
- **External epicardial implant**
- **ICE, TEE, and fluoro guidance**
- **Mechanism of action**
 - Annular reduction
 - AP dimension
 - Cinching
 - Papillary muscle repositioning
 - LV remodeling and stress reduction

Device positioning



Percutaneous Treatment of Mitral Regurgitation

Direct Annuloplasty Approaches

- Multiple techniques using suture/anchor plication, RF thermal contraction of the annulus, or external RF reshaping of an implanted annular ring
- Trans-ventricular approaches using echo and fluoroscopy guidance
- **Companies**
 - Mitralign
 - Guided Delivery Systems
 - Quantumcor
 - Micardia



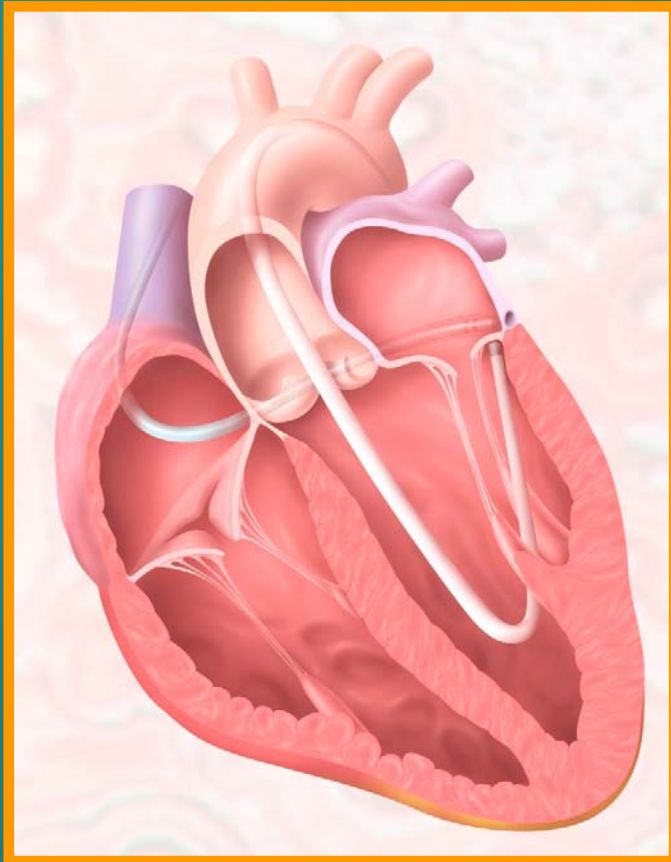
The Mitralign Solution



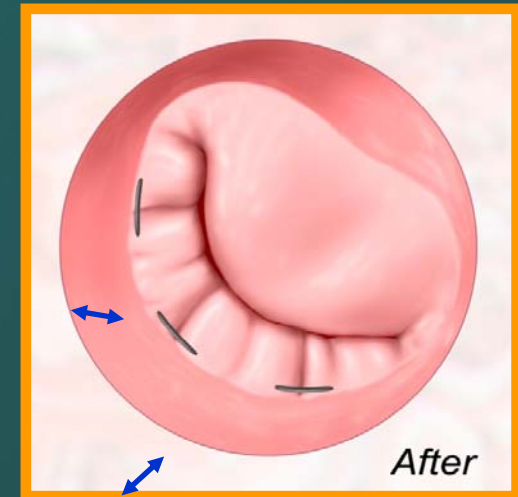
- **Coronary sinus positioning catheter**
- **Central placement (@ P2) of RF-driven trans-annular wire (LV to LA)**
- **Lateral placement of additional RF-driven trans-annular wires**
- **Pledged sutures and lock-up for plication**



Mitralign Direct (suture plication) Annuloplasty System



Trans-ventricular Approach



Before and After Implant Atrial View



Transcatheter Valve Therapy

Final Thoughts - 1

- We are entering a new exciting era: lesser-invasive ***transcatheter treatment of valvular heart disease.***
- There is a ***clear unmet clinical need*** – many patients with valvular heart disease are poorly served with either surgery or medical therapy
- A potpourri of ***innovative devices and concepts*** are being explored focusing on therapies for aortic stenosis and mitral regurgitation.



Transcatheter Valve Therapy

Aortic Stenosis

First Generation Devices



Cribier-Edwards
391 patients



CoreValve
154 patients



Transcatheter Valve Therapy

Mitral Regurgitation

First Generation Devices



Evalve

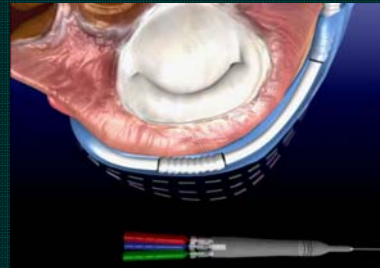


Monarc

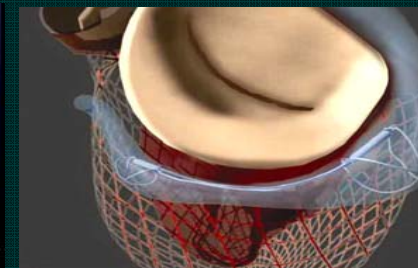
Mobius



Viacor



Carillon



Edge-to-Edge Repair
~200 patients

Coronary Sinus Annuloplasty
~85 patients



Transcatheter Valve Therapy

Final Thoughts - 2

- **Transcatheter AVR** has been performed in ~550 pts worldwide and **proof-of-concept has been validated** with both balloon expandable and self-expanding platforms... **pivotal RCTs** are beginning in the U.S.
- The **multifactorial etiologies of MR** have led to many diverse transcatheter solutions, but **most devices and treatment strategies are still in the formative stages**, with a longer gestation period required to assess performance and plan RCTs.



Transcatheter Valve Therapy

Final Thoughts - 3

- A positive by-product of transcatheter valve therapies has been a rejuvenated working relationship between interventionalists and surgeons; ***a dedicated multidisciplinary team is absolutely essential!***

Stay Tuned!!!

