Is Transcatheter AVR the Standard of Care for High Risk AS Patients? Summary of Worldwide Experiences

Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City

Angioplasty Summit 2009 – TCT Asia Pacific
April 22-24, 2009; Seoul, Korea

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

Presenter Disclosure Information for Angioplasty Summit 2009

Martin B. Leon, M.D.

Scientific Advisory Board or Equity:
Edwards Lifesciences, Medtronic, Sadra

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

Transcatheter AVR

Indications for Surgical AVR

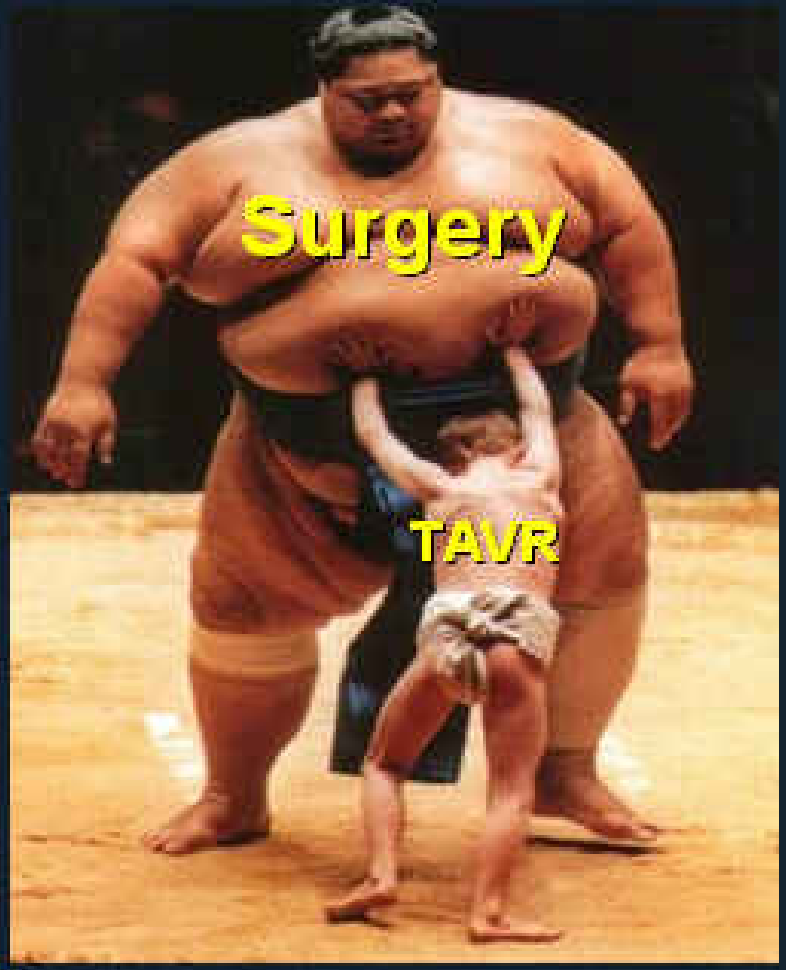
Why is surgical AVR so great?

Because our patients…

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

Transcatheter AVR

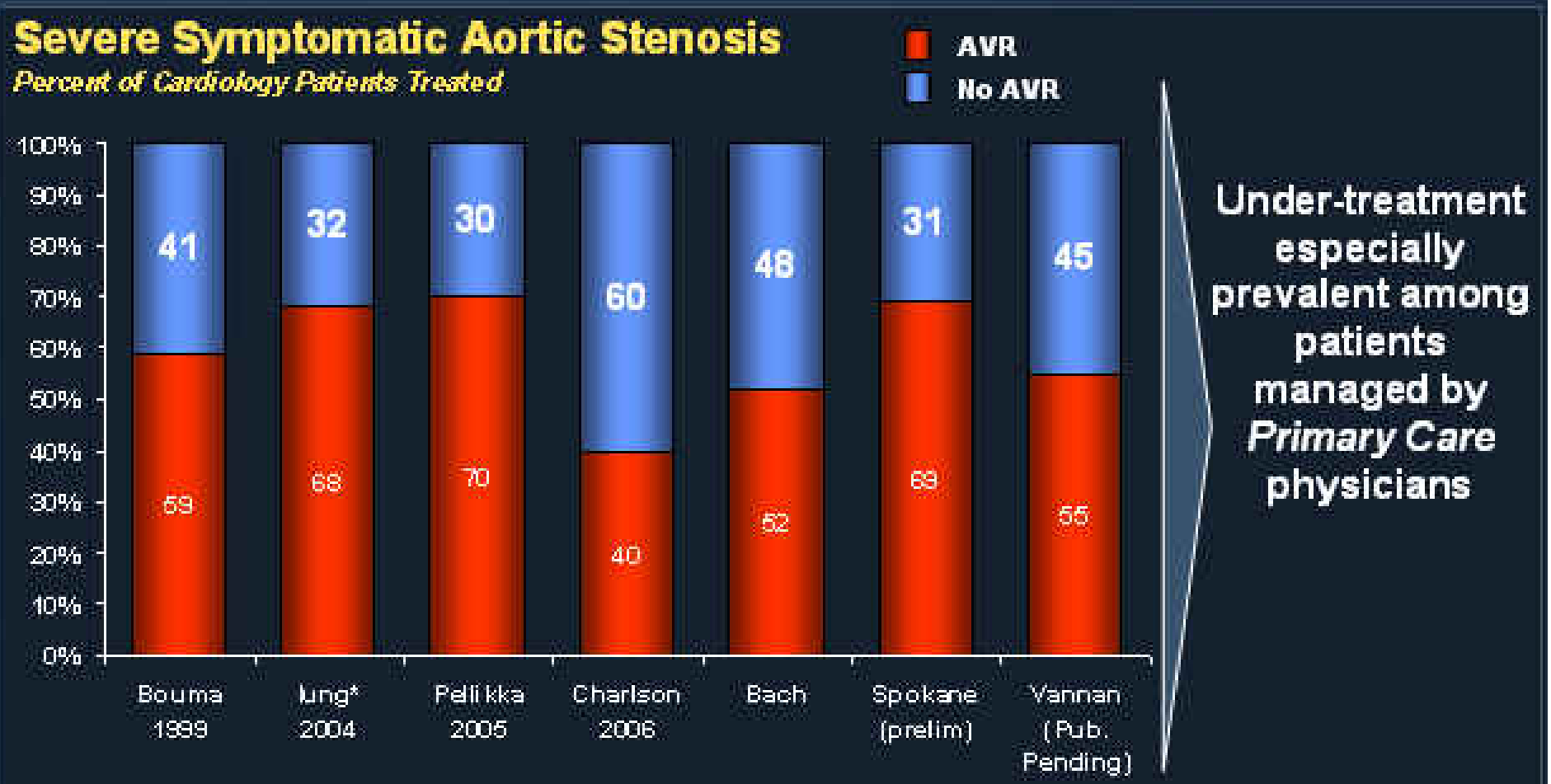
Rules of Engagement



Transcatheter AVR

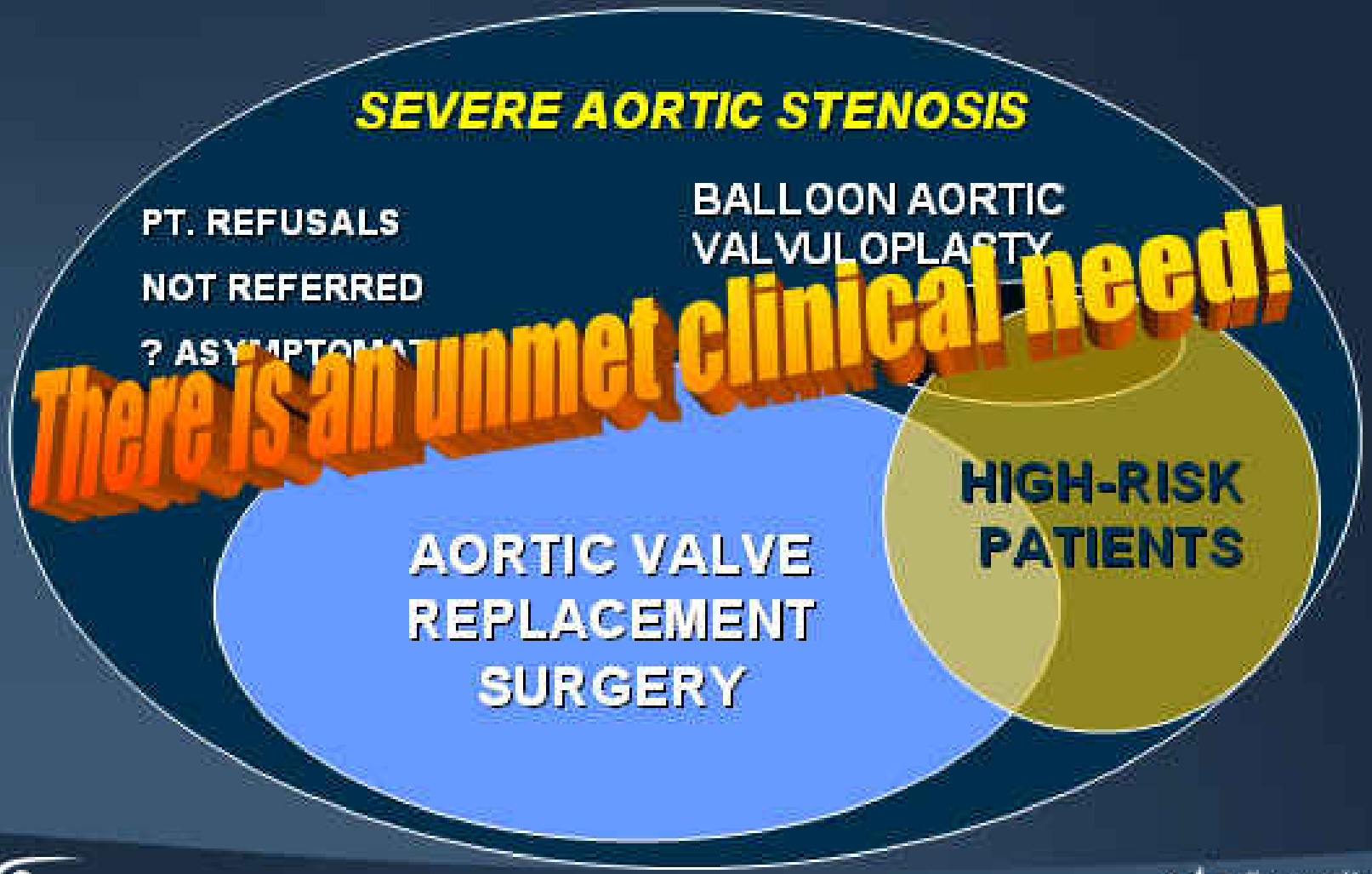
Clinical Indications

At Least 30% of Patients with Severe Symptomatic AS are "Untreated"!



1. Bouma B J et al. To operate or not on elderly patients with aortic stenosis: the decision and its consequences. Heart 1999;82:143-148
2. Iung B et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. European Heart Journal 2003;24:1231-1243 (Includes both Aortic Stenosis and Mitral Regurgitation patients)
3. Pellikka, Sarano et al. Outcome of 622 Adults with Asymptomatic, Hemodynamically Significant Aortic Stenosis During Prolonged Follow-Up. Circulation 2005
4. Charlson E et al. Decision-making and outcomes in severe symptomatic aortic stenosis. J Heart Valve Dis 2006;15:312-321

Potential Patients for Transcatheter Aortic Valve Therapy



CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

Who are the *"High Risk"* AS Patients

- Octogenarians with multiple co-morbidities (COPD, diabetes, ↑creatinine, PVD, ↓LVEF, previous cardiac surgery, others)
- STS Predicted Risk >10%, ~ Logistic EuroSCORE >30% (~15% operative risk @ 30 days)
- Requires close surgical consultation (significant inter-site variability)

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

Who are the *"Inoperable"* AS Patients

- Radiation chest wall/heart disease
- Chest wall deformities (severe)
- End-stage COPD
- Cirrhosis with portal hypertension
- Porcelain aorta (CT proven)
- Degenerative neurocognitive dysfunction
- High "frailty" index (qualitative assessment)
- >50% chance of mortality or never leaving a chronic care facility

Even less perfect formula!
Requires the surgeons acting as the "gatekeepers"!!!

Transcatheter AVR

Clinical Outcomes

TAVR: Clinical Outcomes

What We Know…

What We Need to Know…

TAVR: Clinical Outcomes

What We Know…

What We Need to Know…

Dr. Alain Cribier

First-in-Man PIONEER

Circulation — American Heart Association. Learn and Live.

Percutaneous Transcatheter Implantation of an Aortic Valve Prosthesis for Calcific Aortic Stenosis

First Human Case Description

Alain Cribier, MD; Helene Eltchaninoff, MD; Assaf Bash, PhD; Nicolas Borenstein, MD; Christophe Tron, MD; Fabrice Bauer, MD; Genevieve Derumeaux, MD; Frederic Anselme, MD; François Laborde, MD; Martin B. Leon, MD

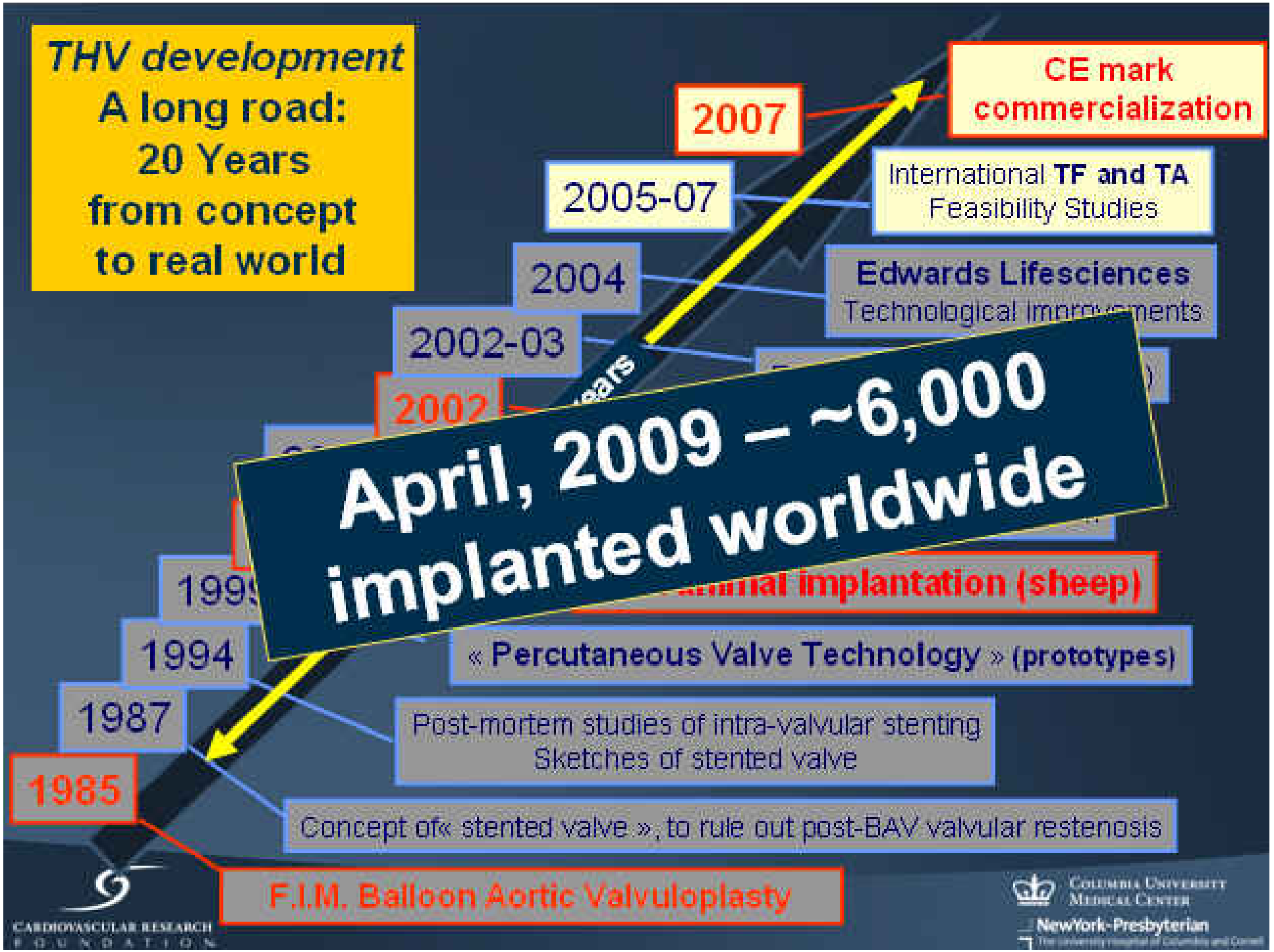
Conclusions— Nonsurgical implantation of a prosthetic heart valve can be successfully achieved with immediate and midterm hemodynamic and clinical improvement.

April 16, 2002

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

NewYork-Presbyterian


THV development
A long road:
20 Years
from concept
to real world
2007
CE mark
commercialization
2005-07
International TF and TA
Feasibility Studies
2004
Edwards Lifesciences
Technological Improvements
2002-03
April, 2009 – ~6,000
implanted worldwide
1994
« Percutaneous Valve Technology » (prototypes)
1987
Post-mortem studies of intra-valvular stenting
Sketches of stented valve
1985
Concept of« stented valve », to rule out post-BAV valvular restenosis
F.I.M. Balloon Aortic Valvuloplasty
CARDIOVASCULAR RESEARCH
FOUNDATION
COLUMBIA UNIVERSITY
MEDICAL CENTER
NewYork-Presbyterian

Transcatheter AVR

Current Generation Devices

Edwards
~3,000 patients

CoreValve
~3,000 patients

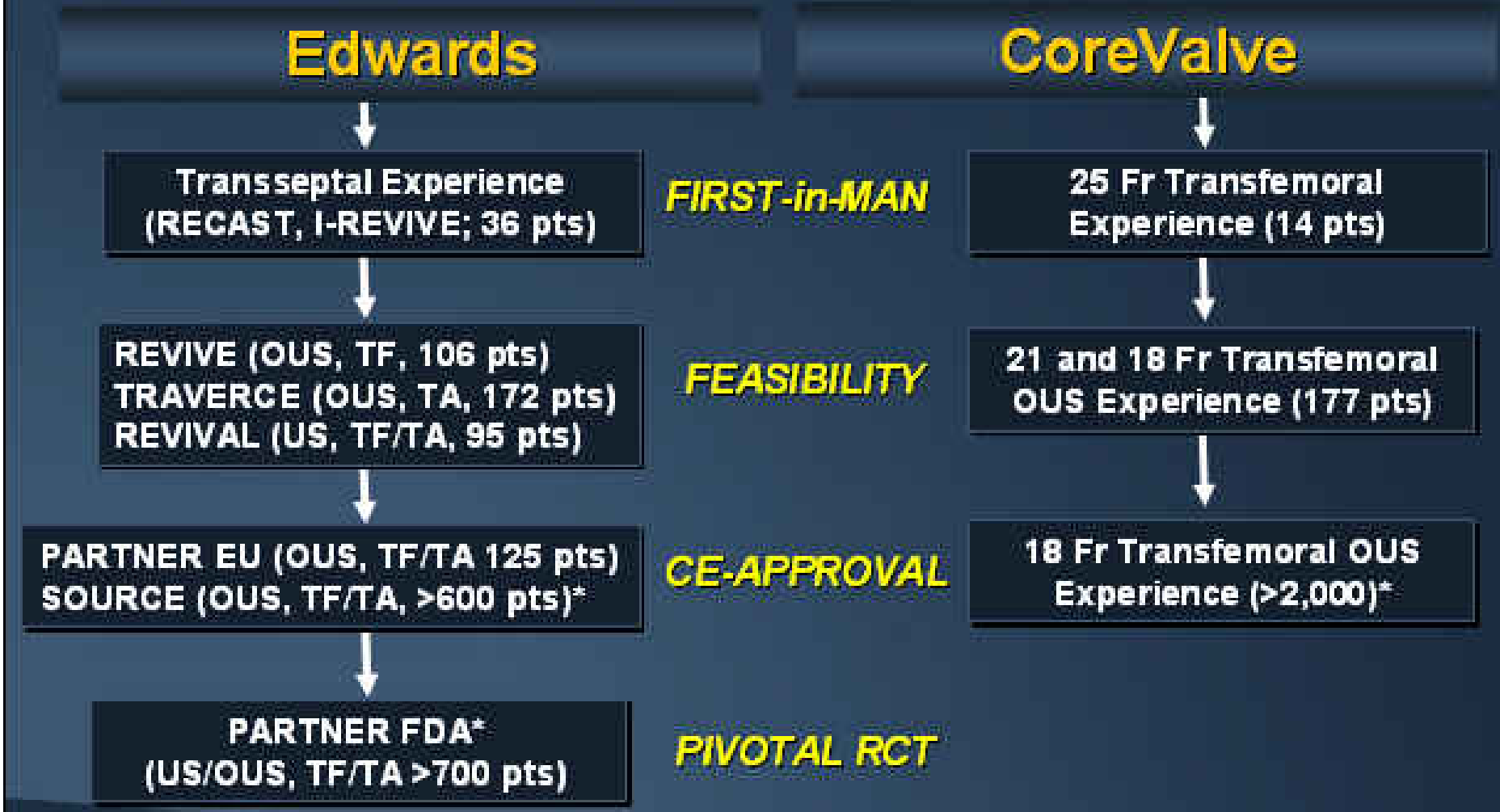
TAVR: Clinical Evidence

Clinical Data Conundrum…

- Early clinical trials chaotic, reflecting frequent changes in technology, procedural methods, and data collection processes (small sample sizes and difficult to pool or compare datasets)
- Study endpoints not clarified or standardized (e.g. vascular complications, peri-valvular AR)
- Inconsistent use of data coordinating centers, core labs and CECs
- Poor long-term follow-up of essential valve-related endpoints (e.g. FU echoes)
- ***All problems exaggerated due to complexity and acuity of patient population!***

Transcatheter AVR

Clinical Data Sources



* still enrolling patients

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

REVIVE & REVIVAL (n=161)

Patient Demographics

Age (yrs)	83.5 ± 5.9 (66 - 96)
≥ 90 years	14.3% (23)
≥ 80 years	75.2% (121)
Female	52.5% (84)
Ejection Fraction (echo)	50.1 ± 16.6%
Pre-AVA (cm^2 – echo)	0.57 ± 0.13
Mean gradient (mmHg) echo	43.4 ± 17.0
CHF - Mean NYHA Class	3.24 ± 0.63
Angina	41.0% (66)
Syncope	14.3% (23)
Mean Logistic EuroSCORE	30.7% ± 15.2
Mean STS Score (REVIVAL Only)	13.1% ± 7.2

REVIVE + REVIVAL

High Risk Co-morbidities

Prior Cardiac Surgery	28.6% (46)
Prior Coronary Intervention	24.2% (39)
History of CVA or TIA	16.1% (26)
COPD	27.3% (44)
Peripheral vascular disease	20.5% (33)
Chronic Renal Disease	21.7% (35)
Diabetes	26.1% (42)
Porcelain Aorta	6.2% (10)
Chest Wall Radiation	6.8% (11)
Chest Wall Deformities	4.3% (7)

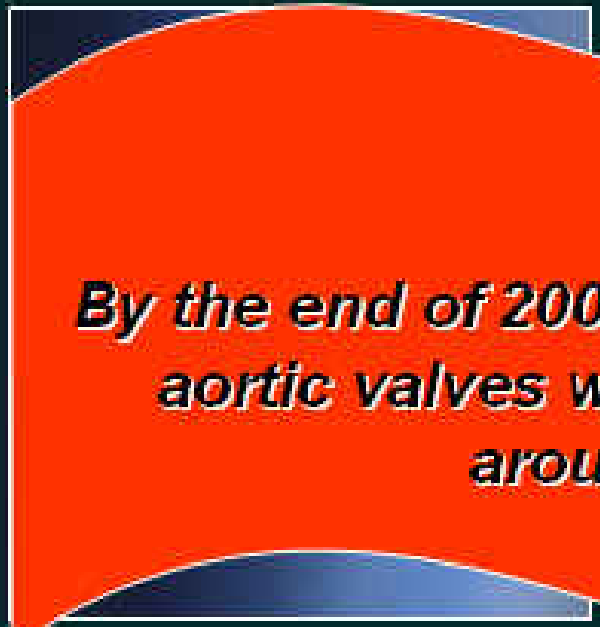
TAVR: Clinical Outcomes

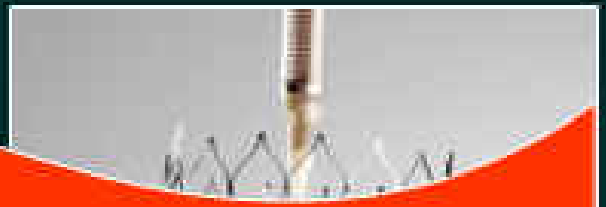
What We Know…

- **TAVR has become very popular, with surprising clinical penetration soon after CE approval and commercial release**

Transcatheter AVR

Current Generation Devices





By the end of 2009, > 16,000 transcatheter aortic valves will have been implanted around the world!

Edwards
~3,000 patients

~3,000 patients

Transcatheter AVR

Medtronic

$325 million

NEWS RELEASE

Contacts:
Daniel Beach — Public Relations — 763-505-2603
Jeff Warren — Investor Relations — 763-505-2696

FOR IMMEDIATE RELEASE

MEDTRONIC ACQUIRES VENTOR TECHNOLOGIES LTD.

Medtronic Targets Leadership Role in Aortic Transcatheter Valves

Ventor

CoreValve

Medtronic

$1,200 million

NEWS RELEASE

Contacts:
Daniel Beach — Public Relations — 763-505-2603
Jeff Warren — Investor Relations — 763-505-2696

FOR IMMEDIATE RELEASE

MEDTRONIC TO ACQUIRE COREVALVE, INC.

Medtronic Targets Leadership Role in High-Growth Aortic Transcatheter Valves

Press releases: Feb 23, 2009

TAVR: Clinical Outcomes

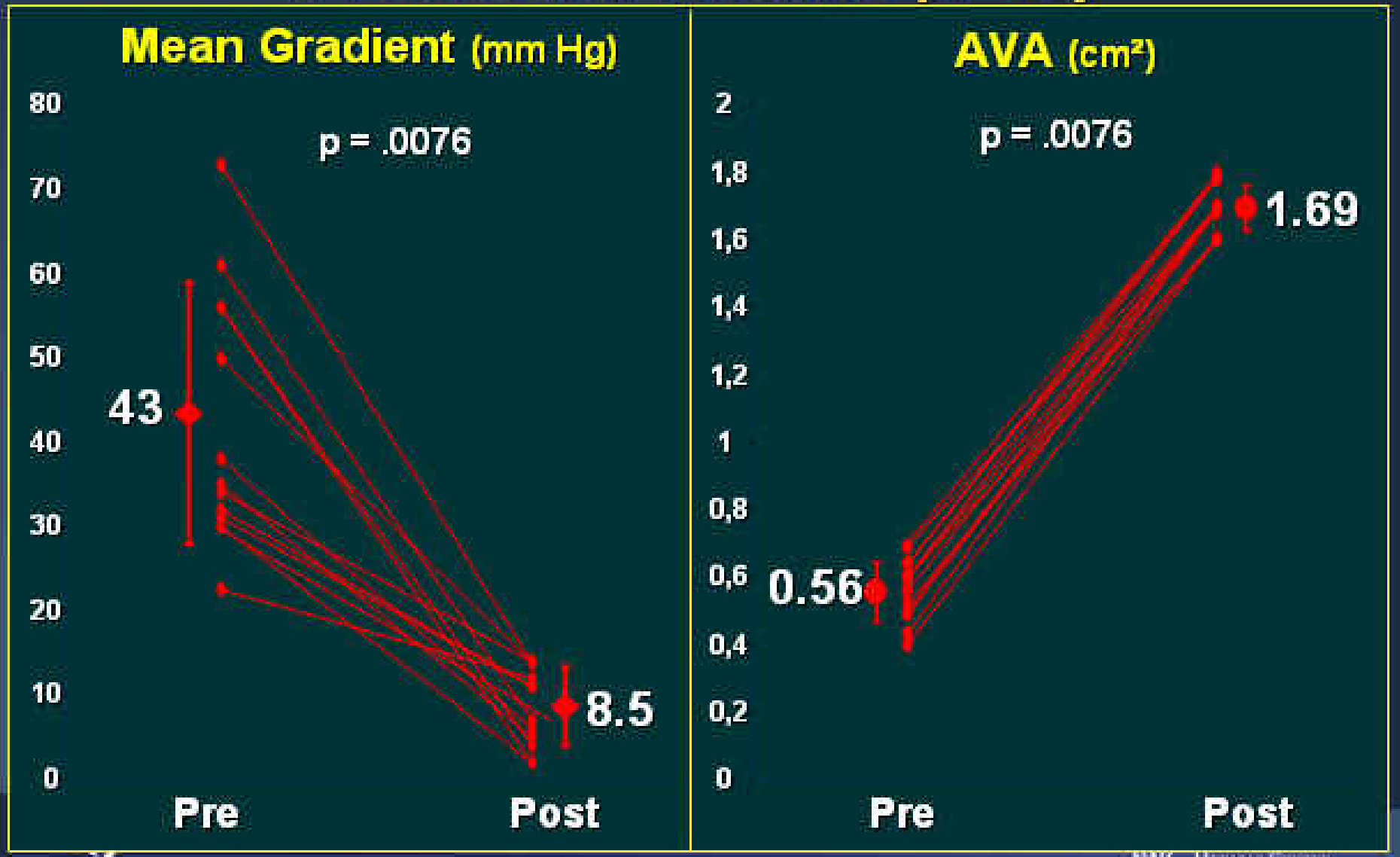
What We Know…

- TA-AV has become very popular, with surprising clinical penetration soon after CE approval and commercial release

- **Acute and medium-term hemodynamic performance of catheter-based biologic valves is equivalent to surgically implanted valves**

Cribier – Early PHV Experiences

Procedural Results (n=16)

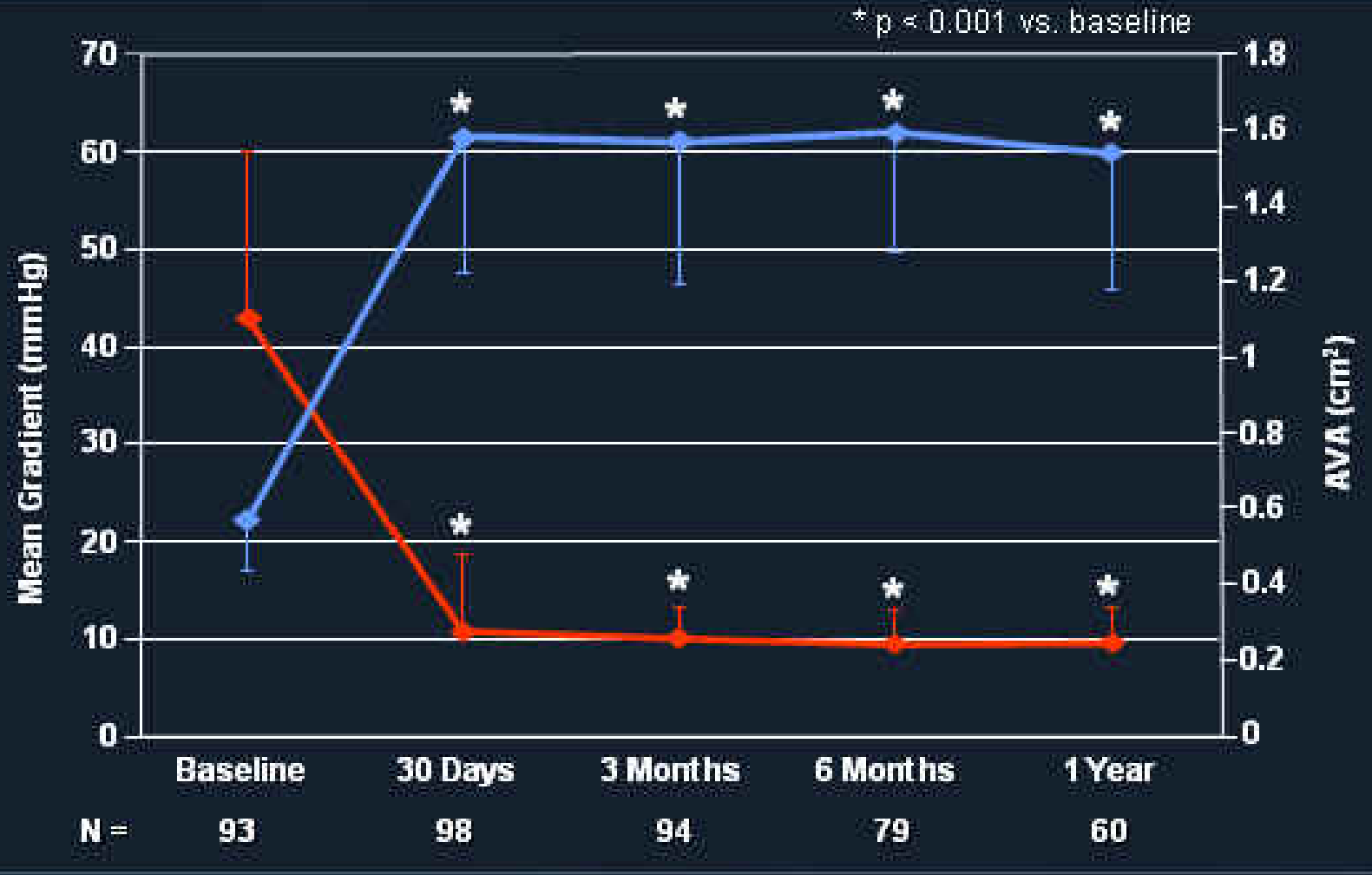


CARDIOVASCULAR RESEARCH FOUNDATION

NewYork-Presbyterian

REVIVE + REVIVAL

Changes in Echo Gradient and EOA



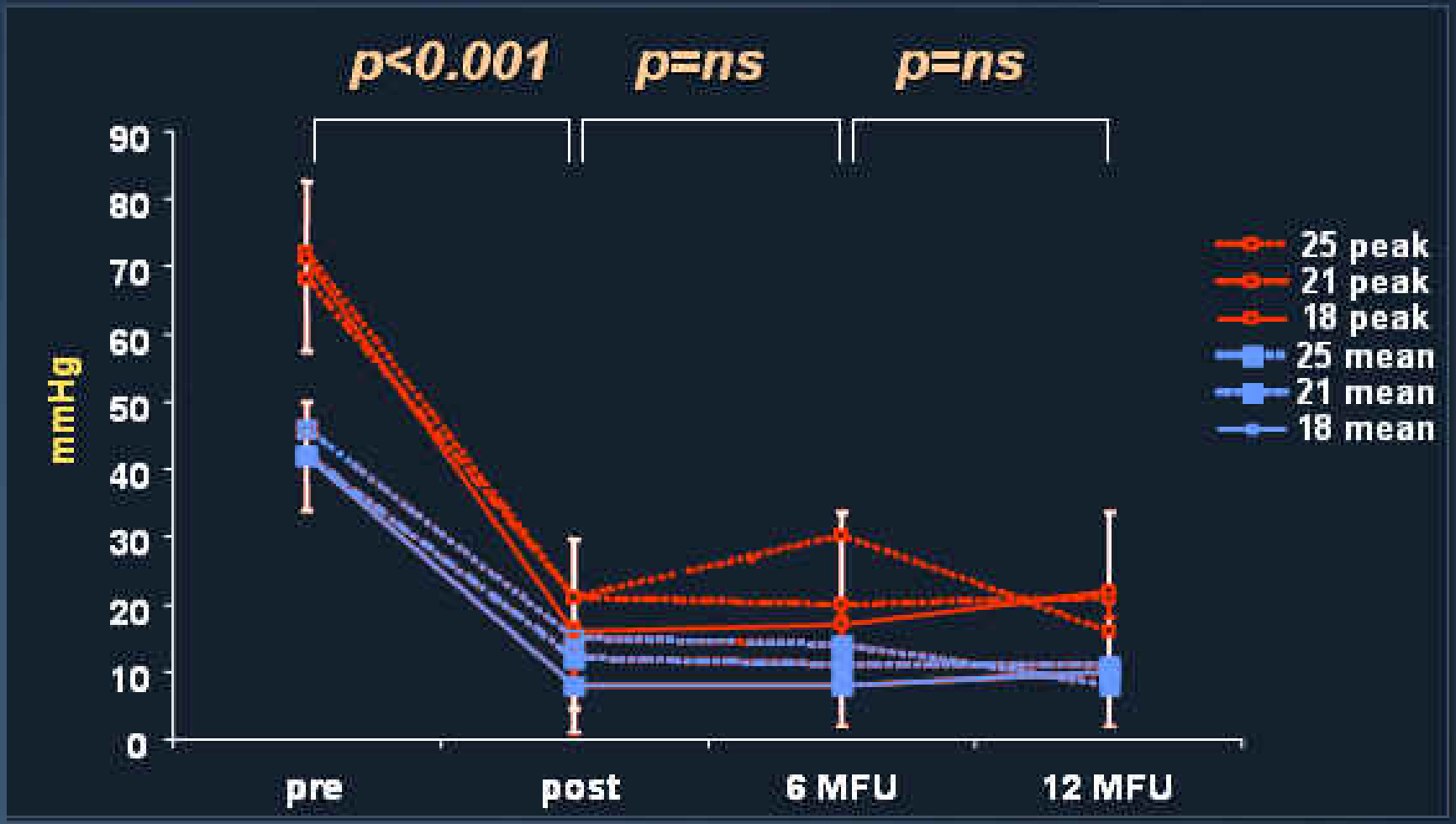
*Echo Core Lab Data
+/- 1 SD

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

CoreValve Siegburg Experience*

Transvalvular peak and mean pressure gradients



* Consecutive Enrollment until March 2008

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

TAVR: Clinical Outcomes

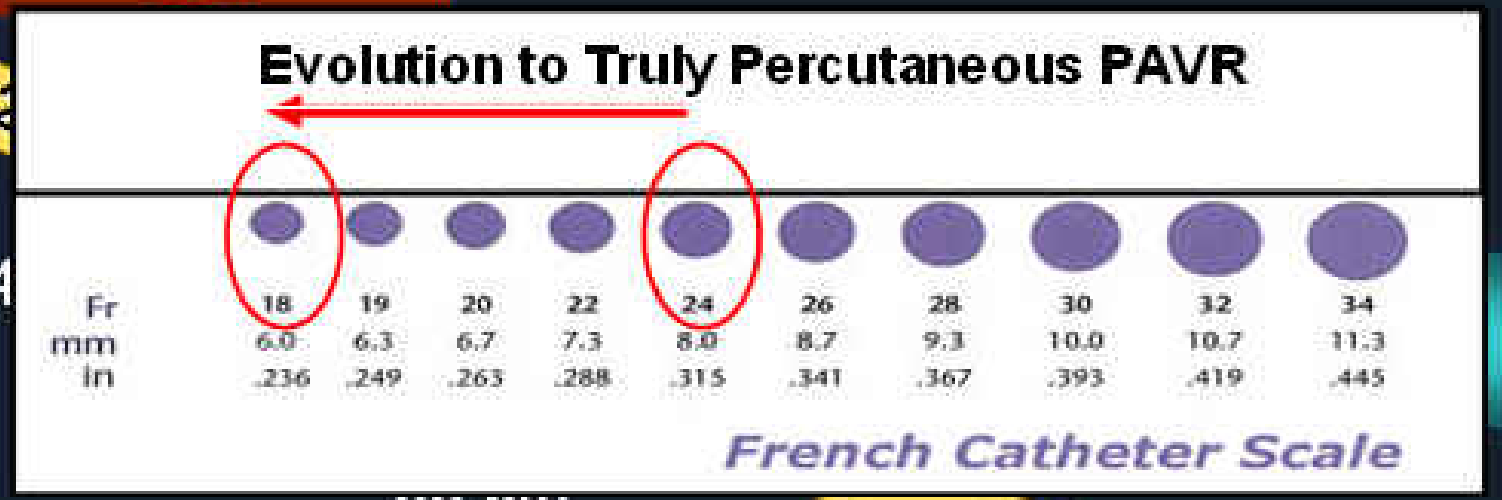
What We Know…

- TAVR has become very popular, with surprising clinical penetration soon after CE approval and commercial release
- Acute and intermediate-term hemodynamic performance of catheter-based bioprosthetic valves is equivalent to surgically implanted valves
- **TAVR devices have evolved significantly and the procedures have become simplified**

CoreValve Procedural Progress

Evolution to a
"real cath lab procedure"
within first 40 Pts of 18 Fr study

Generation 1
25F



14

Oct. 2006

>2,500 pts

CoreValve *ReValving* System

Delivery Catheter Evolution

GEN1
8mm

GEN2
7mm

GEN3
6mm
(18 Fr)

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

The Current Generation
Edwards – SAPIEN THV

Bovine Tissue
ThermaFix Treatment
Pericardial Mapping
Leaflet Deflection
Proprietary Processing

New
Skirt Height

Edwards-SAPIEN THV

Untreated Equine
Tissue

Current
Skirt Height

Cribier-Edwards THV

The Next Generation
Edwards – SAPIEN XT THV

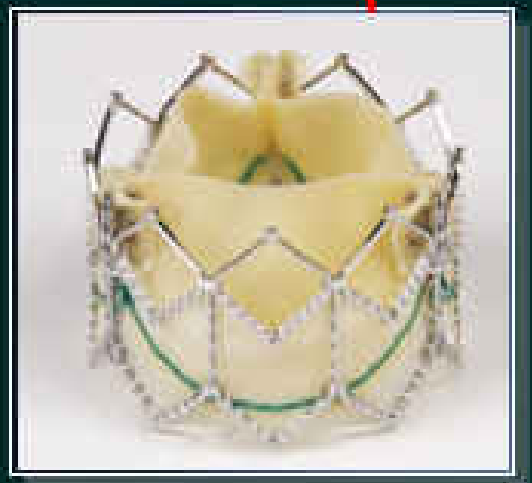
Bovine Tissue
ThermaFix Treatment
Pericardial Mapping
Leaflet Deflection
Proprietary Processing

Edwards-SAPIEN THV

New
Skirt Height

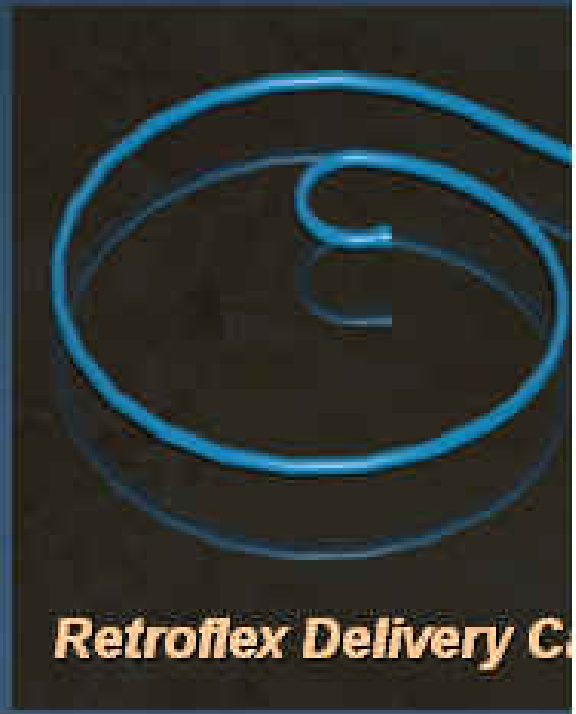
New Sizes
(20,23,26,29mm)

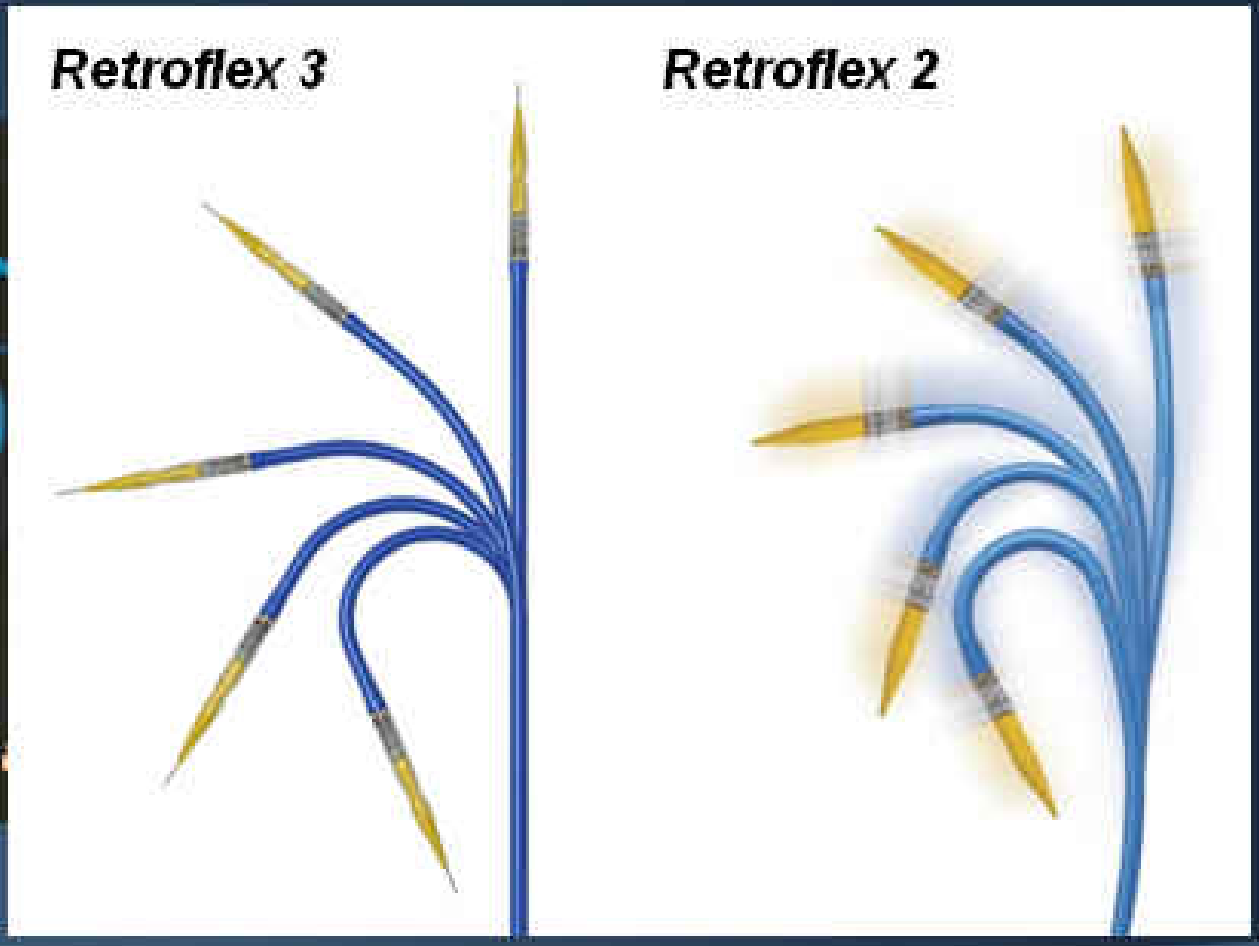
Cobalt Alloy Frame
New Leaflet Geom
(improved durability)



SAPIEN XT THV

Edwards *Flex Cath*
Delivery System Evolution

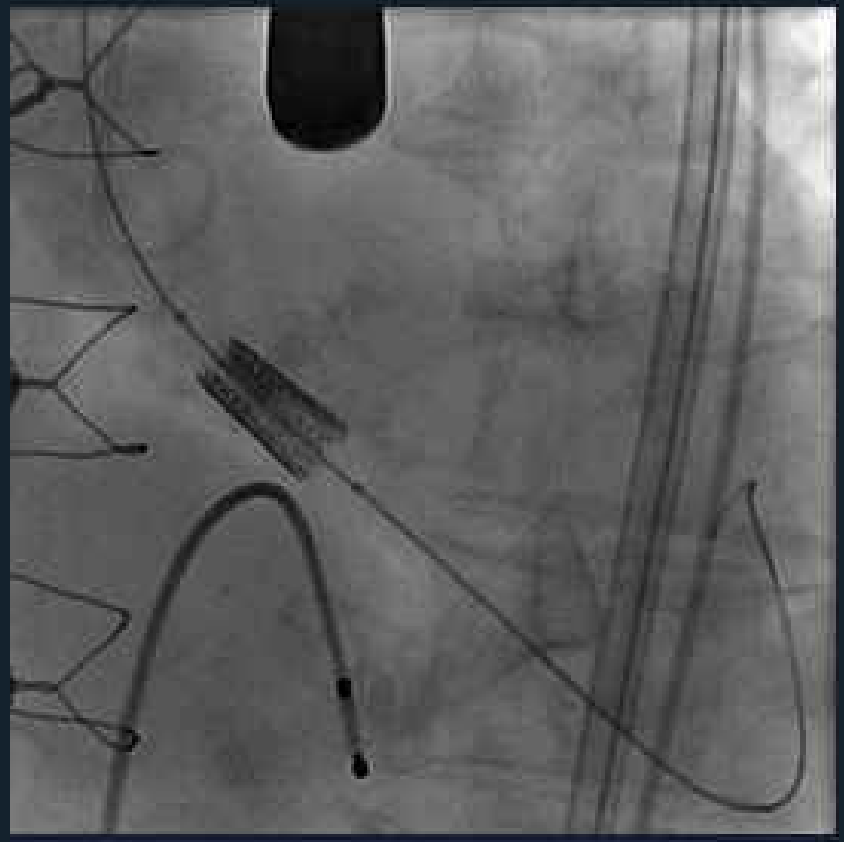




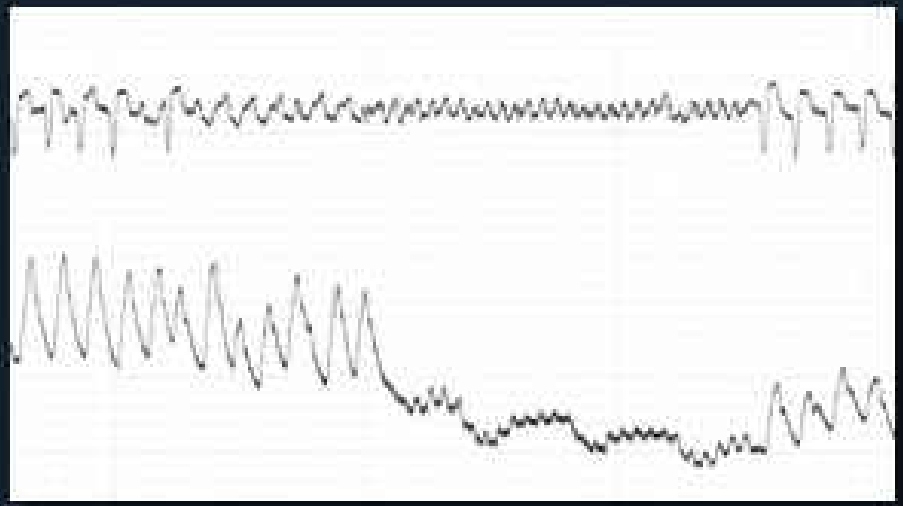
CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

Retrograde Trans-femoral Edwards Aortic Valve Deployment



Rapid pacing : 220/min



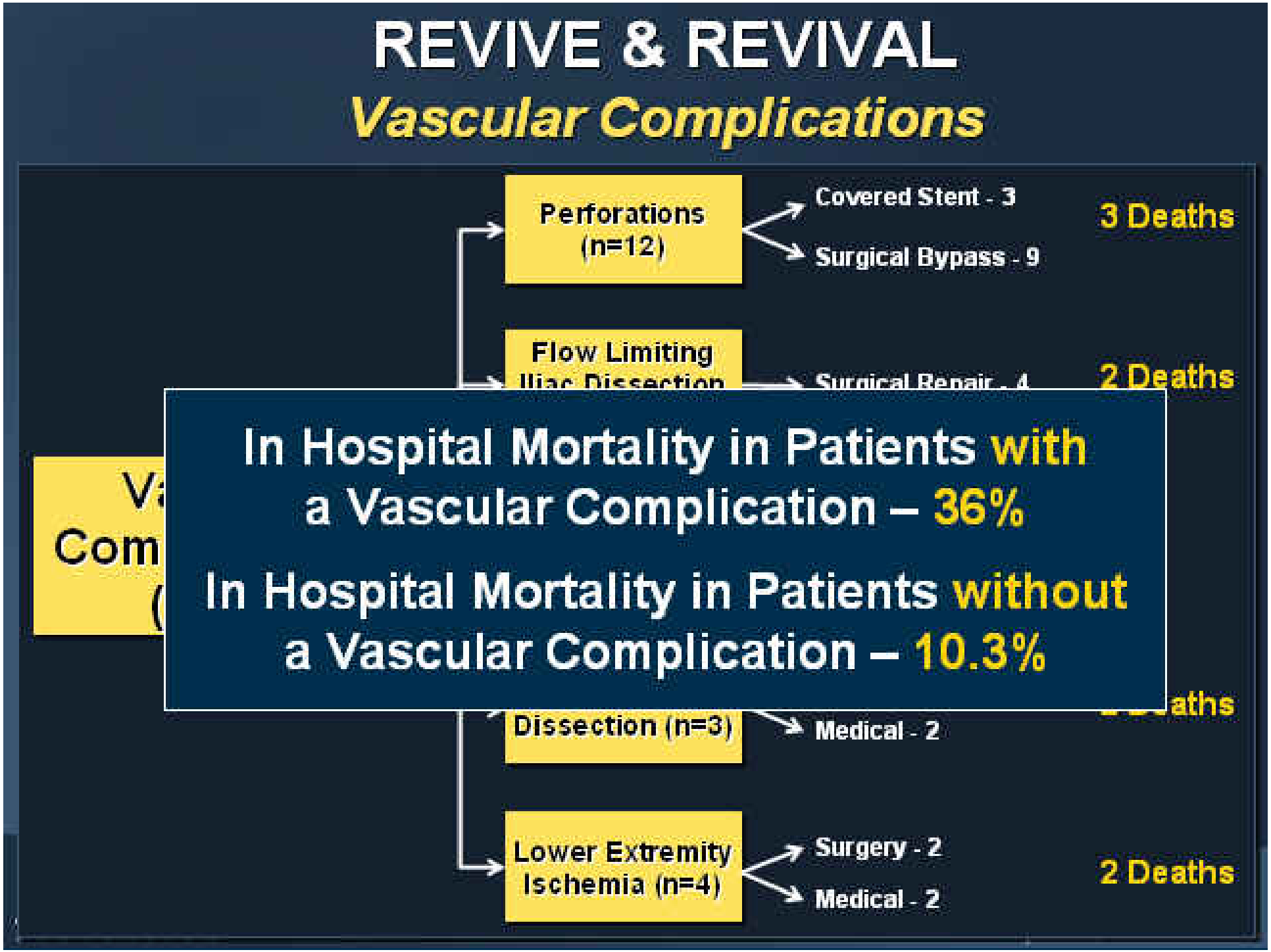
TAVR: Clinical Outcomes

What We Know…

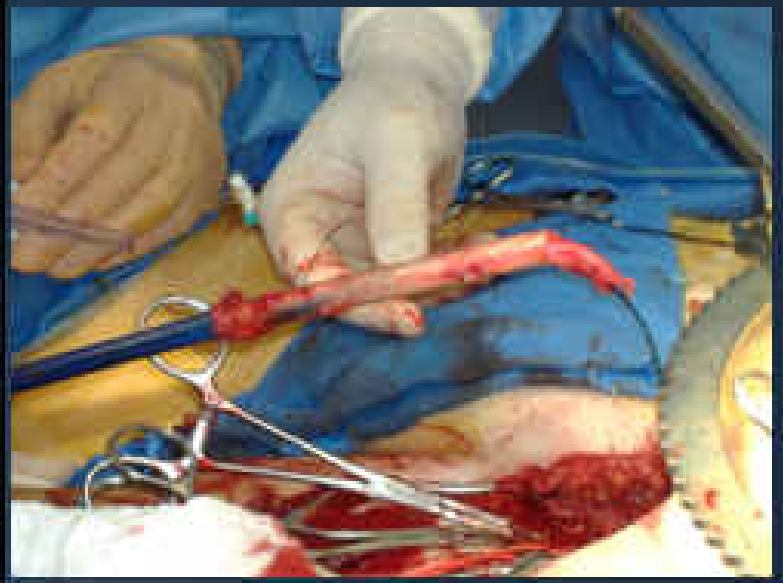
- TAVR has become very popular, with surprising clinical penetration soon after CE approval and commercial release
- Acute and medium-term hemodynamic performance of catheter-based biologic valves is equivalent to surgically implanted valves
- TAVR devices have evolved significantly and the procedures have become simplified
- **Important "new" procedural complications have emerged with TAVR**

REVIVE & REVIVAL

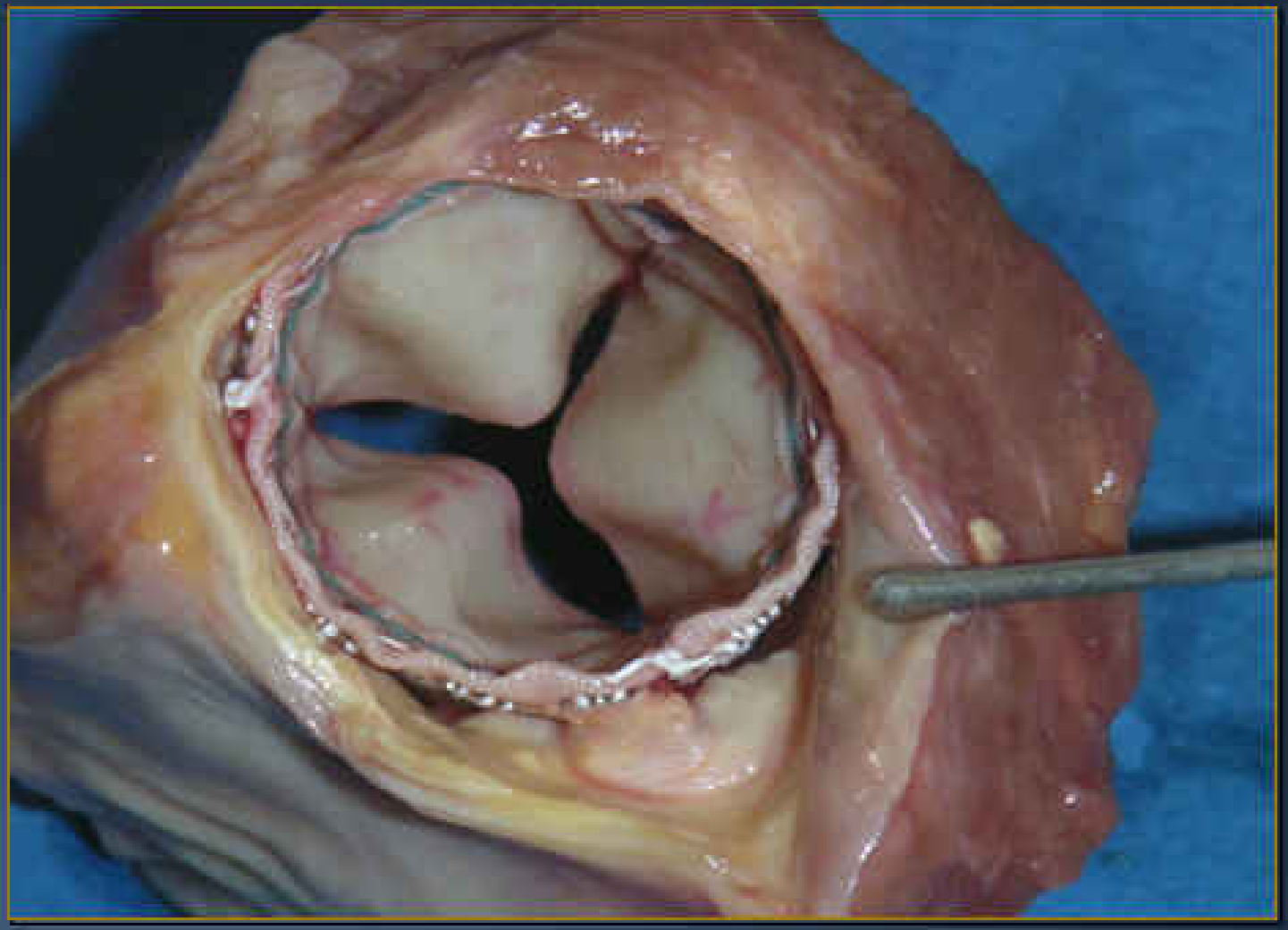
Vascular Complications



Iliac Perforation



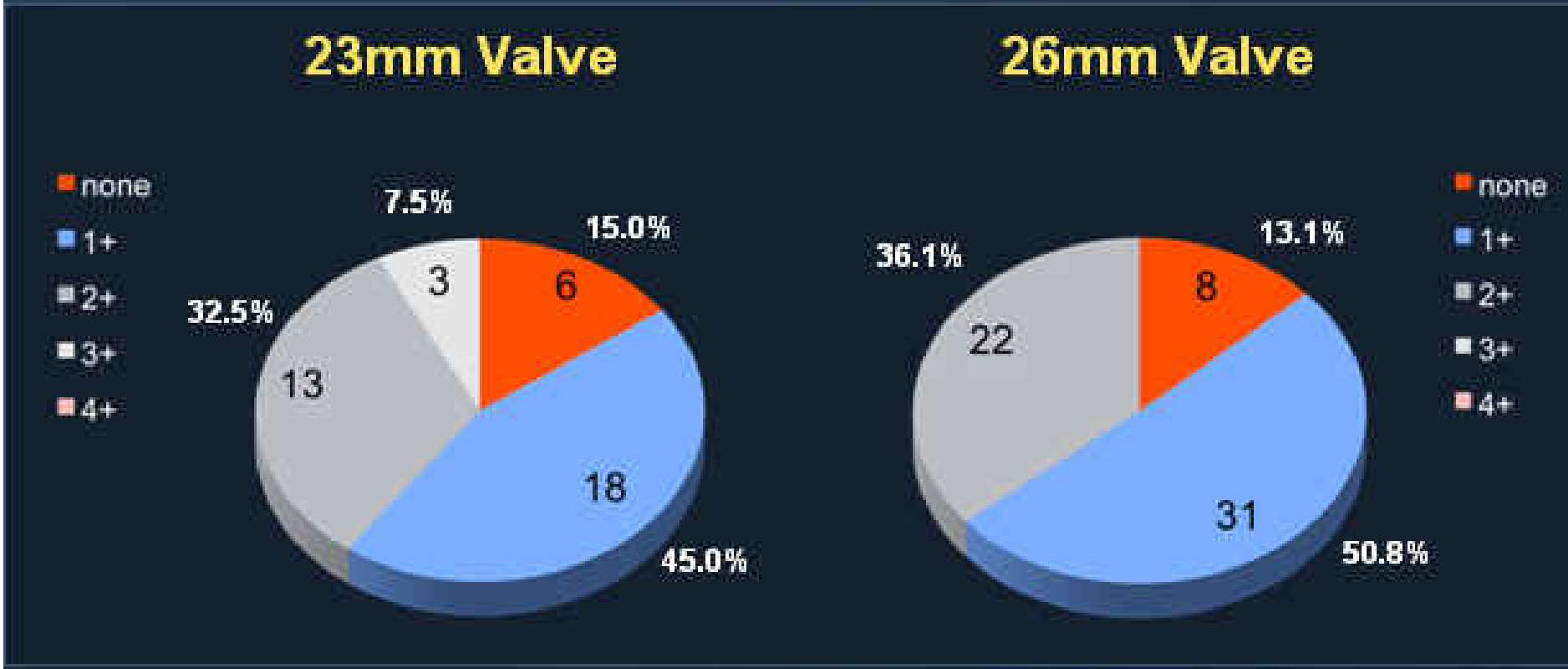
Peri-valvular Regurgitation



Patient #5

REVIVE + REVIVAL

Aortic Regurgitation after TAVR



No patient that received a 26mm valve had > 2+ post-procedure AR

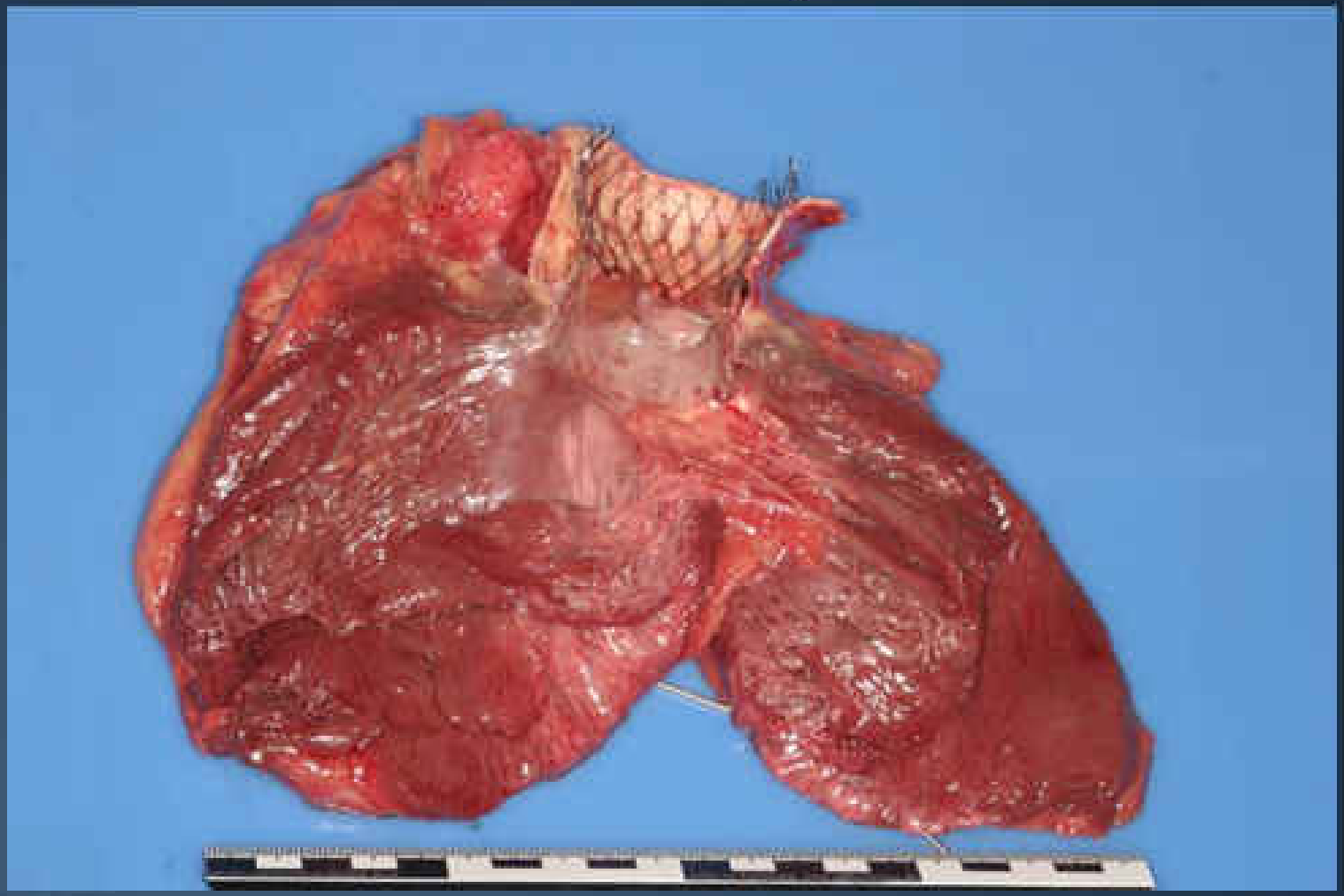
* Echo Core Lab

Left Main Coronary Occlusion

(VF and SD after implant)

High implant, low left coronary ostia, long leaflet with bulky calcified nodules

AV-Block III° Following COREVALVE Implantation



CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

NewYork-Presbyterian

AV-Block III° Following COREVALVE Implantation

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

CoreValve Siegburg Experience
In-hospital Outcome

	25 French (n=10)	21 French (n=24)	18 French (n=102)
Death, n [%]	4 [40.0]	2 [8.3]	10 [9.8]
Stroke, n [%]	1 [10.0]	2 [8.3]	3 [2.9]
Major, n [%]	1 [10.0]	0	1 [1.0]
Minor, n [%]	0	2 [8.3]	2 [2.0]
Myocardial infarction, n [%]	0	1 [4.2]	2 [2.0]
Pacemaker requiring, n [%]	*1 [10.0]*	*3 [13.6]*	*30 [33.3]*
MACCE, n [%]*	4 [40.0]	5 [20.8]	14 [13.7]

CoreValve: Other ≤ 30-Day Adverse Events*
(Site Reported & Non-Adjudicated)

	In-Training	Solo	Total EER
CARDIAC Deaths†	6.9%	6.8%	6.9%
Aortic Dissection	0.7%	0.4%	0.6%
Cardiac Tamponade	3.9%	2.5%	3.4%
Cardiac Perforation	2.9%	1.8%	2.5%
Access Site Complication	2.3%	0.6%	1.7%
Major Bleeding	5.2%	3.7%	4.6%
Conversion to Surgery	0.6%	1.0%	0.7%
Myocardial Infarction	0.9%	0.4%	0.7%
Major Arrhythmia	9.0%	4.7%	7.4%
Pacemaker	*18.9%*	*18.0%*	*18.6%*
Renal Failure	1.8%	2.0%	1.9%
Stroke	2.2%	2.3%	2.2%
TIA	0.3%	0.4%	0.4%

CARDIOVASCULAR RESEARCH FOUNDATION

* Multiple events in same patients = data not cumulative
† Includes deaths where cause is not known

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

TAVR: Clinical Outcomes

What We Know…

- TA-VI has become very popular, with surprising clinical penetration soon after CE approval and commercial release
- Acute and medium-term hemodynamic performance of catheter-based biologic valves is equivalent to surgically implanted valves
- TA-VI devices have evolved significantly and the procedures have become simplified
- Important "new" procedural complications have emerged with TA-VI

- **Clinical outcomes at 30 days and one year were associated with high "all cause" mortality**

REVIVE & REVIVAL
Clinical Outcomes

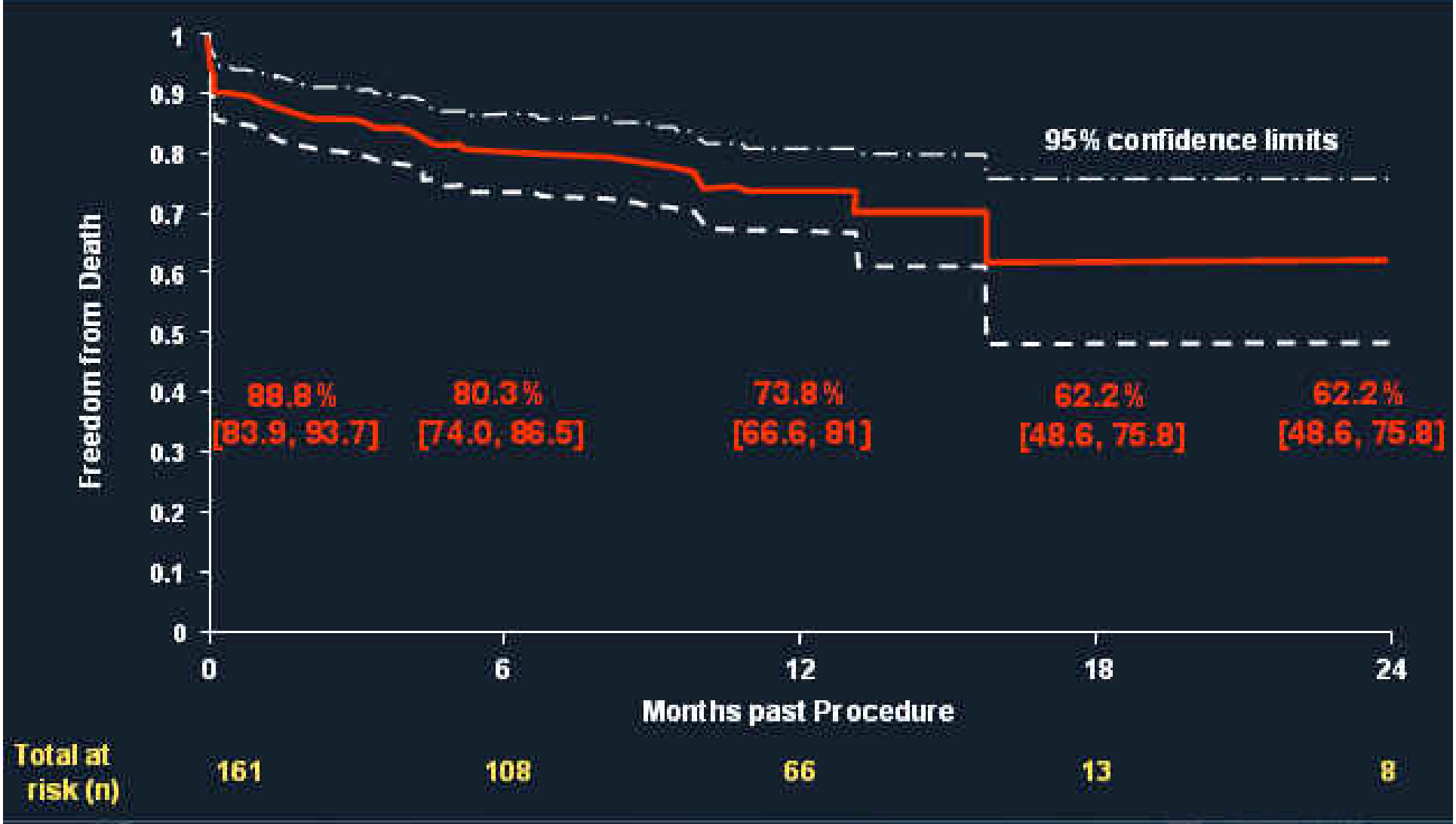
	≤ 30 days	> 30 days *	Total
MACCE	29 (18.6%)	26 (16.8%)	52 (32.3%)
Death	18 (11.2%)	26 (16.1%)	44 (27.3%)
MI	5 (3.1%) **	1 (0.6%) **	6 (3.7%) **
Stroke	7 (4.3%)	3 (1.9%)	10 (6.2%)
Major	4 (2.5%)	3 (1.9%)	7 (4.3%)
Minor	3 (1.9%)	0	3 (1.9%)
Urgent Cardiac Surgery	2 (1.2%)	0	2 (1.2%)

* F/U – mean 9.8 months (median 11.9 months, max. 27.3 months)

** MI defined as CK-MB or Trop > 3 times normal + ECG changes or symptoms

REVIVE & REVIVAL

Cumulative Survival

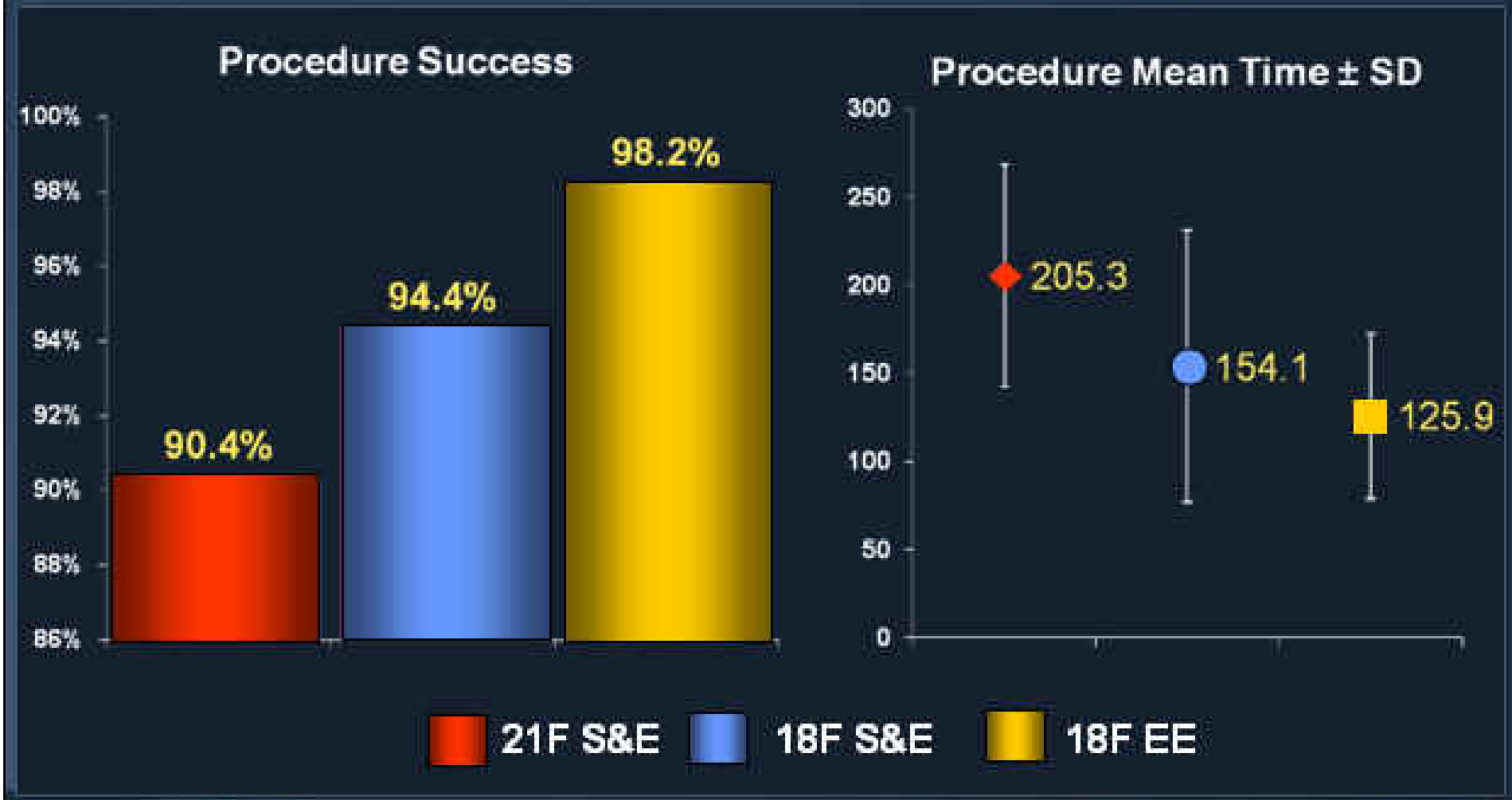


TAVR: Clinical Outcomes

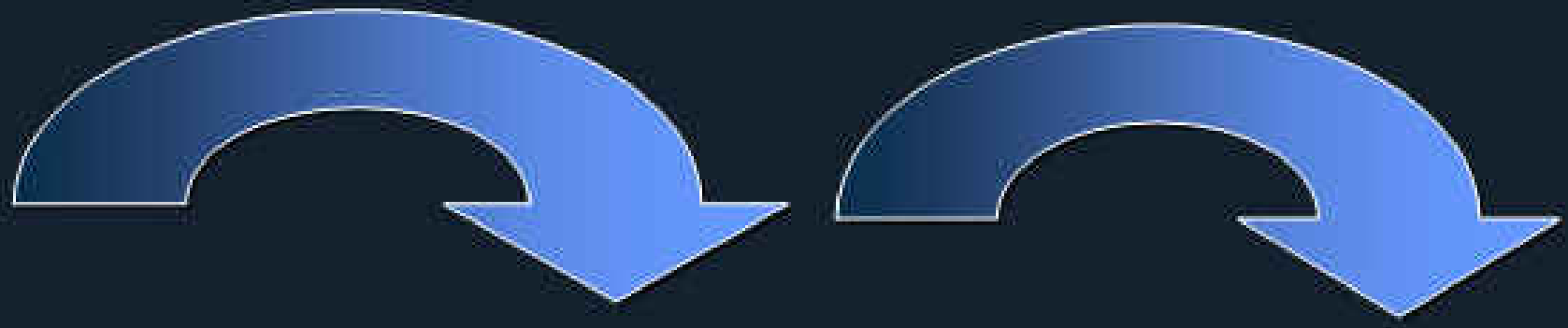
What We Know…

- **Over time, with improved devices and procedure technique, better case selection, and rigorous physician training, TAVR outcomes have improved**

CoreValve: Procedural Results



REVIVE improved screening to reduce vascular complications



Vascular Access Complication Rate, by patient
January 2006 – June 2006
30%

Vascular Screening with Columbia University Medical Center Core Lab INSTITUTED (in coordination with DSMB)

Vascular Access Complication Rate, by patient
August 2006 – December 2007
5.8%

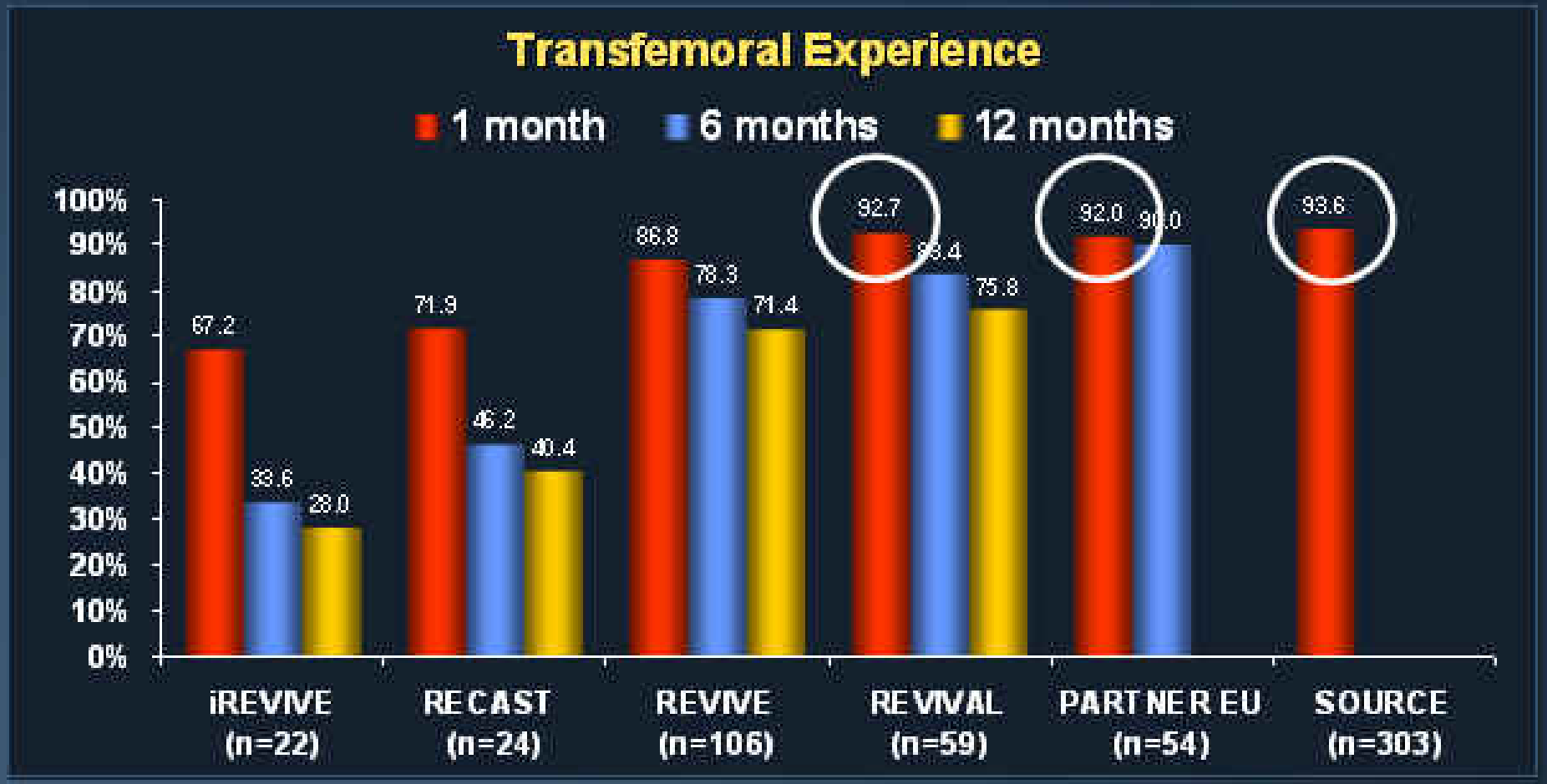
P = .006

CARDIOVASCULAR RESEARCH FOUNDATION

NewYork-Presbyterian
The University Hospital of Columbia and Cornell

Transcatheter AVR

Survival at 1, 6 and 12 months



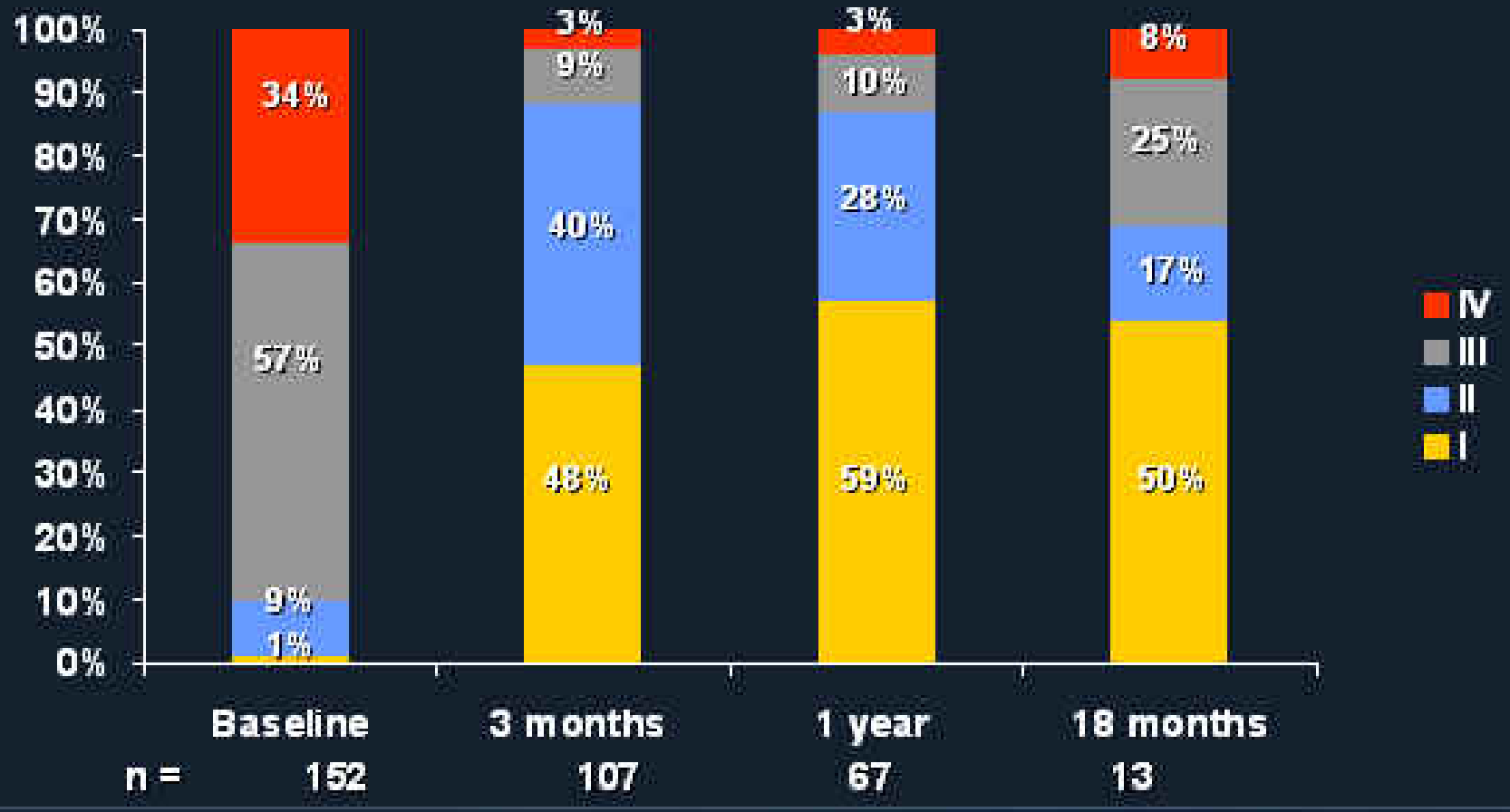
TAVR: Clinical Outcomes

What We Know…

- Over time, with improved devices and procedure technique, better case selection, and rigorous physician training, TAVR outcomes have improved
- **TAVR survivors have marked improvement in all symptom-based clinical efficacy parameters – there is dramatic uniform incremental benefit in QOL metrics!**

REVIVE + REVIVAL

Changes in NYHA Class



90% patients at baseline NYHA Class III/IV,
87% of patients surviving to one year are NYHA Class I/II

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

TAVR: Clinical Outcomes

What We Know…

What We Need to Know…

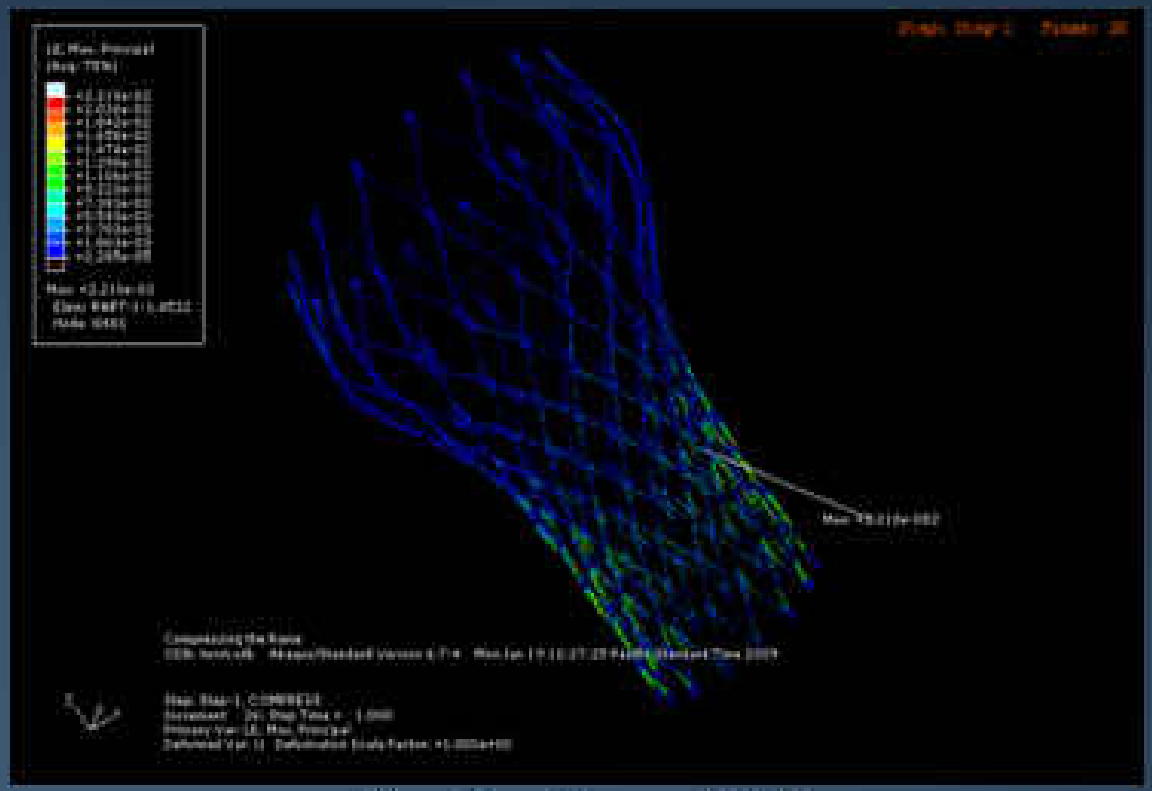
TAVR: Clinical Outcomes

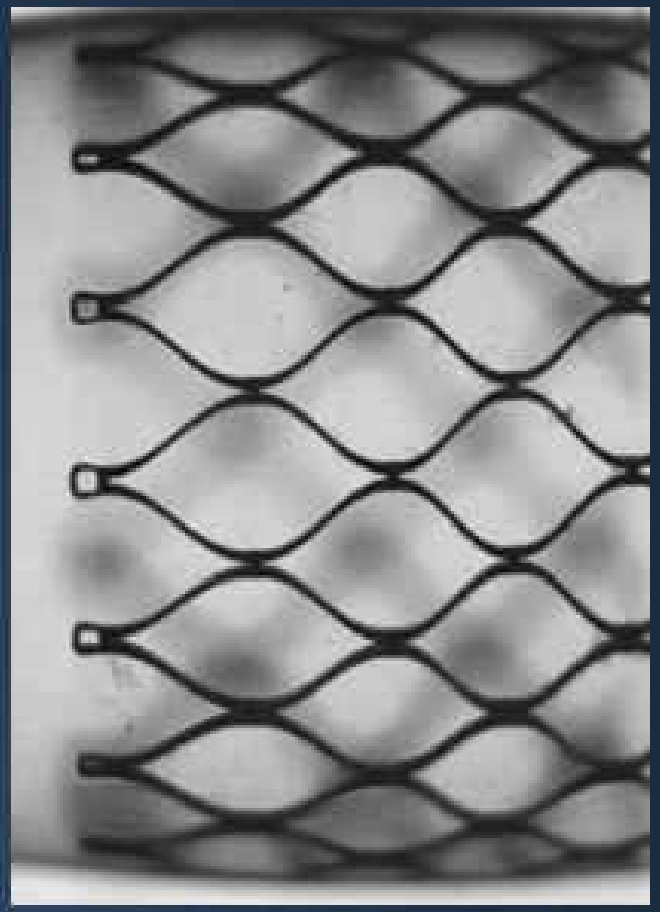
What We Need to Know…

- **Long-term valve and platform durability (late valve failure and late integrity of platform; ? clinical consequences)**

"Test to Fatigue" Studies:

Higher Distention and Rotation Beyond Physiologic Conditions





Xiao-Yan Gong, Ph.D.
Medical Implant Mechanics LLC

Transcatheter AVR - Durability

4 year FU specimen

Edwards
~3,000 patients

Courtesy of Dr. William O'Neill

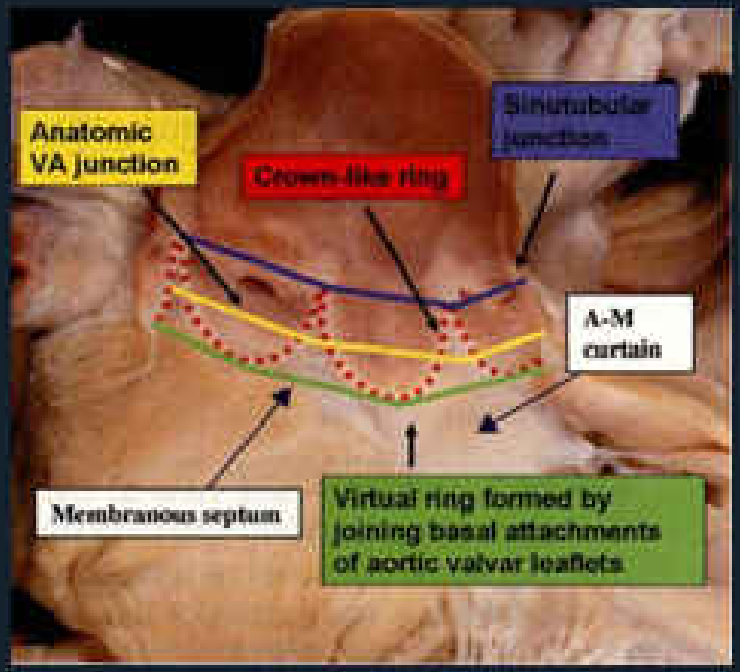
TAVR: Clinical Outcomes

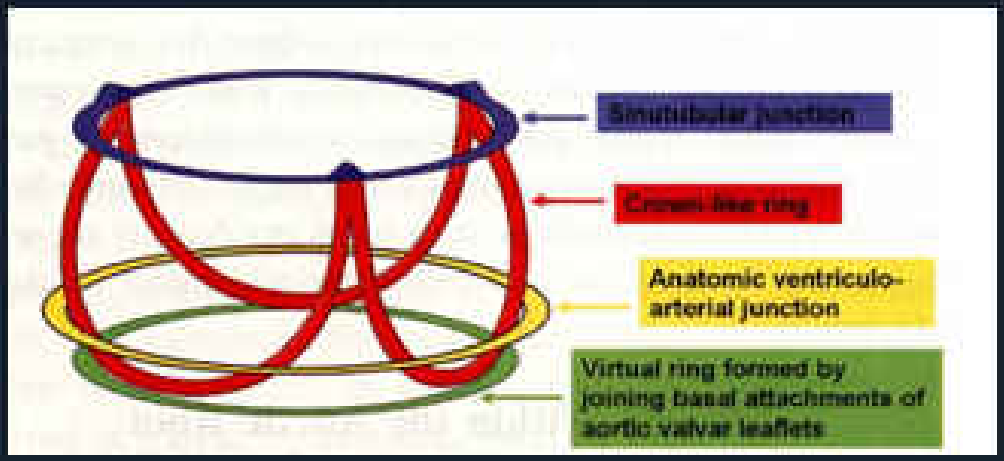
What We Need to Know…

- Long-term valve and platform durability (late valve failure and late integrity of platform + clinical consequences)
- **Late clinical complications – impact of mild-mod peri-valvular AR, effects on coronaries (disease progression), Rx of CAD, MV dysfunction, etc.**

The Aortic Valvar Complex

Complex anatomic relationships





Diseased aortic valve leaflets in close proximity to…

- ***aortic root (annulus)***
- ***coronary ostia***
- ***sinuses of Valsalva***
- ***anterior mitral leaflet***
- ***membranous septum (AVN)***
- ***LV outflow tract***

Piazza et al, *Circ Cardiovasc Intervent.* 2008;1:74-81

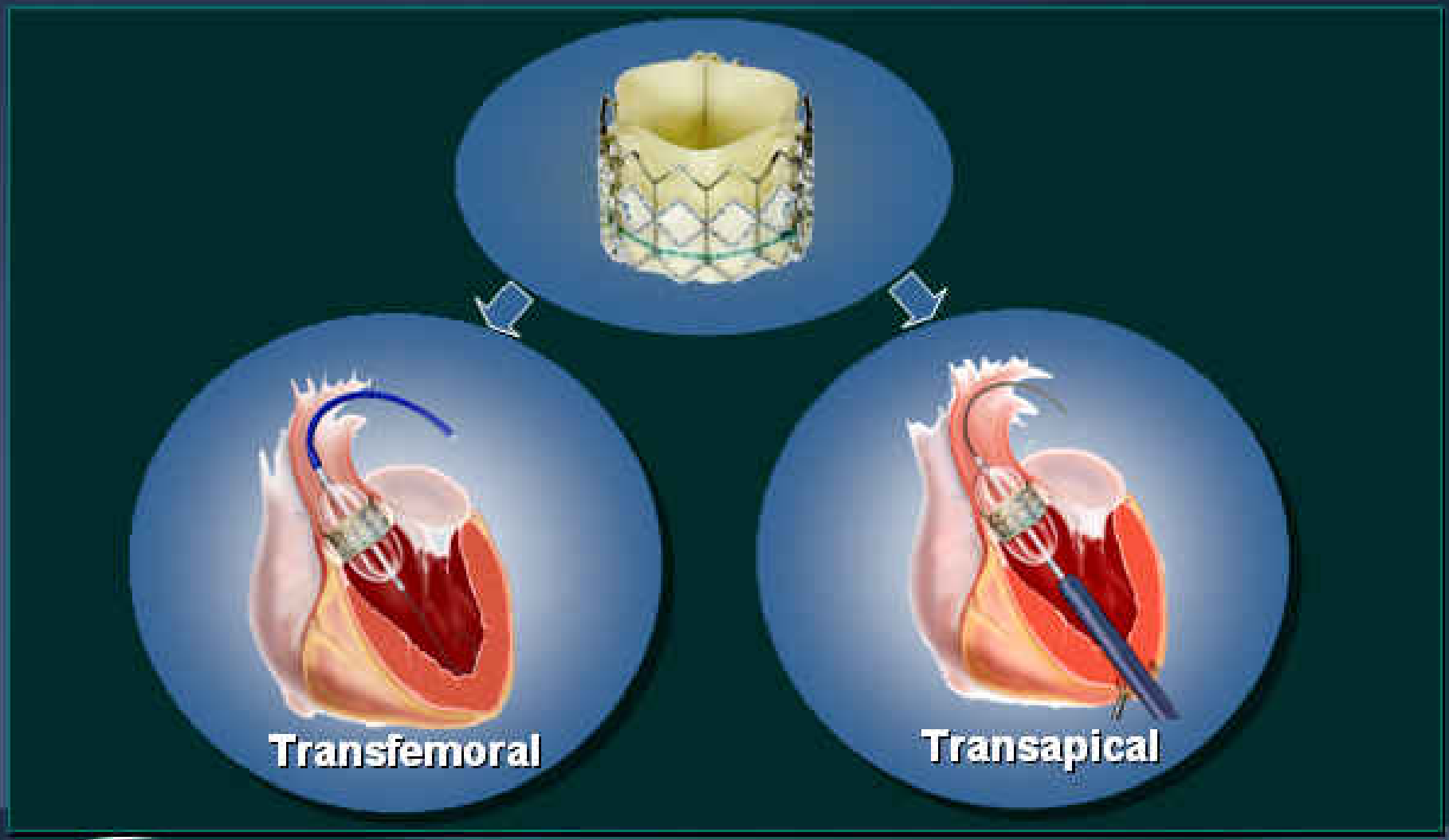
TAVR: Clinical Outcomes

What We Need to Know…

- Long-term valve and platform durability (late valve failure and late integrity of platform + clinical consequences)
- Late clinical complications – impact of mild-mod peri-valvular L.R. effect on coronaries (disease progression, PCI of CAD, LV dysfunction, etc.
- **Relative value and preference of trans-apical vs. trans-femoral (vs. other) approaches**

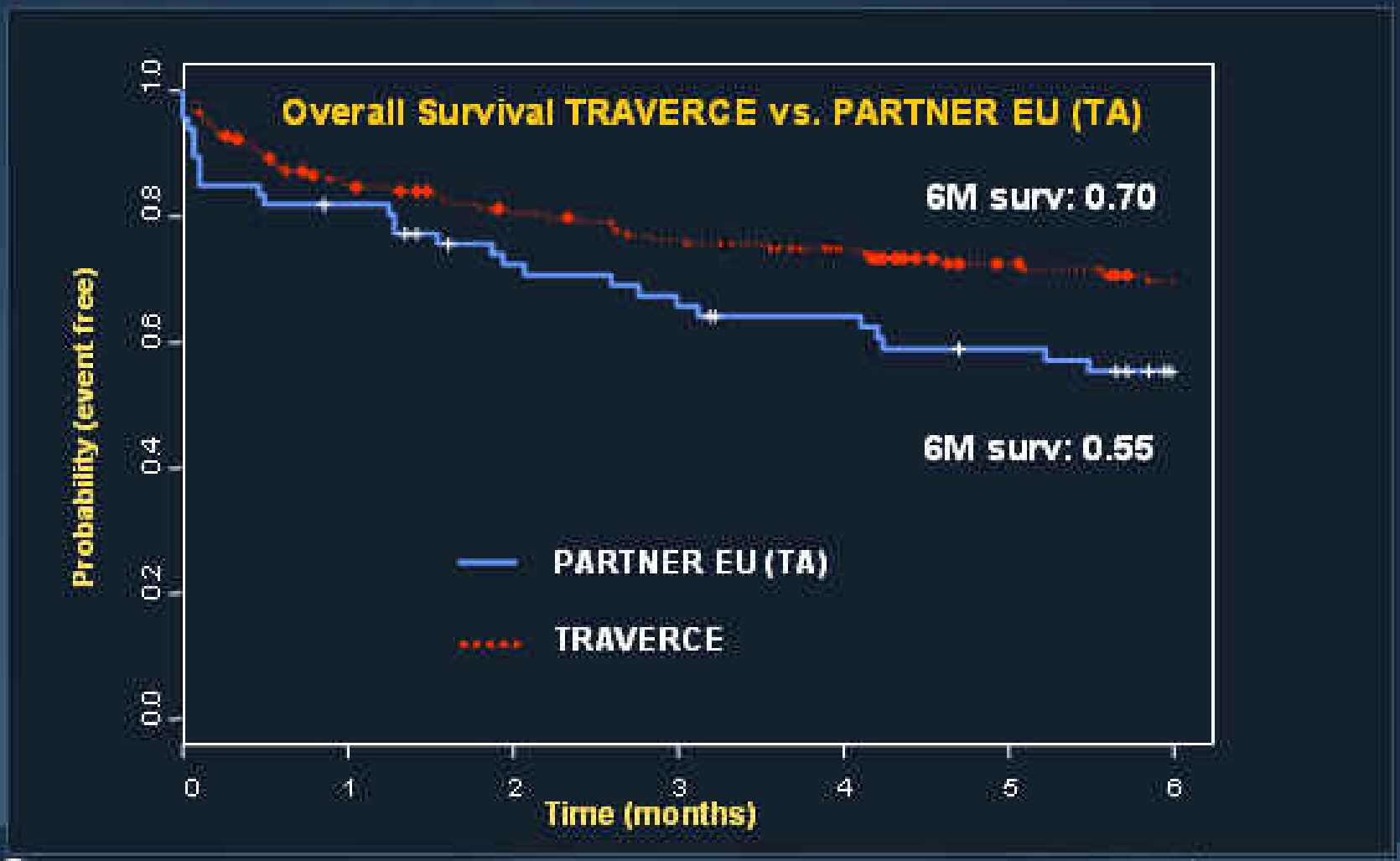
Transcatheter AVR

Transapical Access Route



TA Survival

PARTNER EU & TRAVERCE



CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER

NewYork-Presbyterian

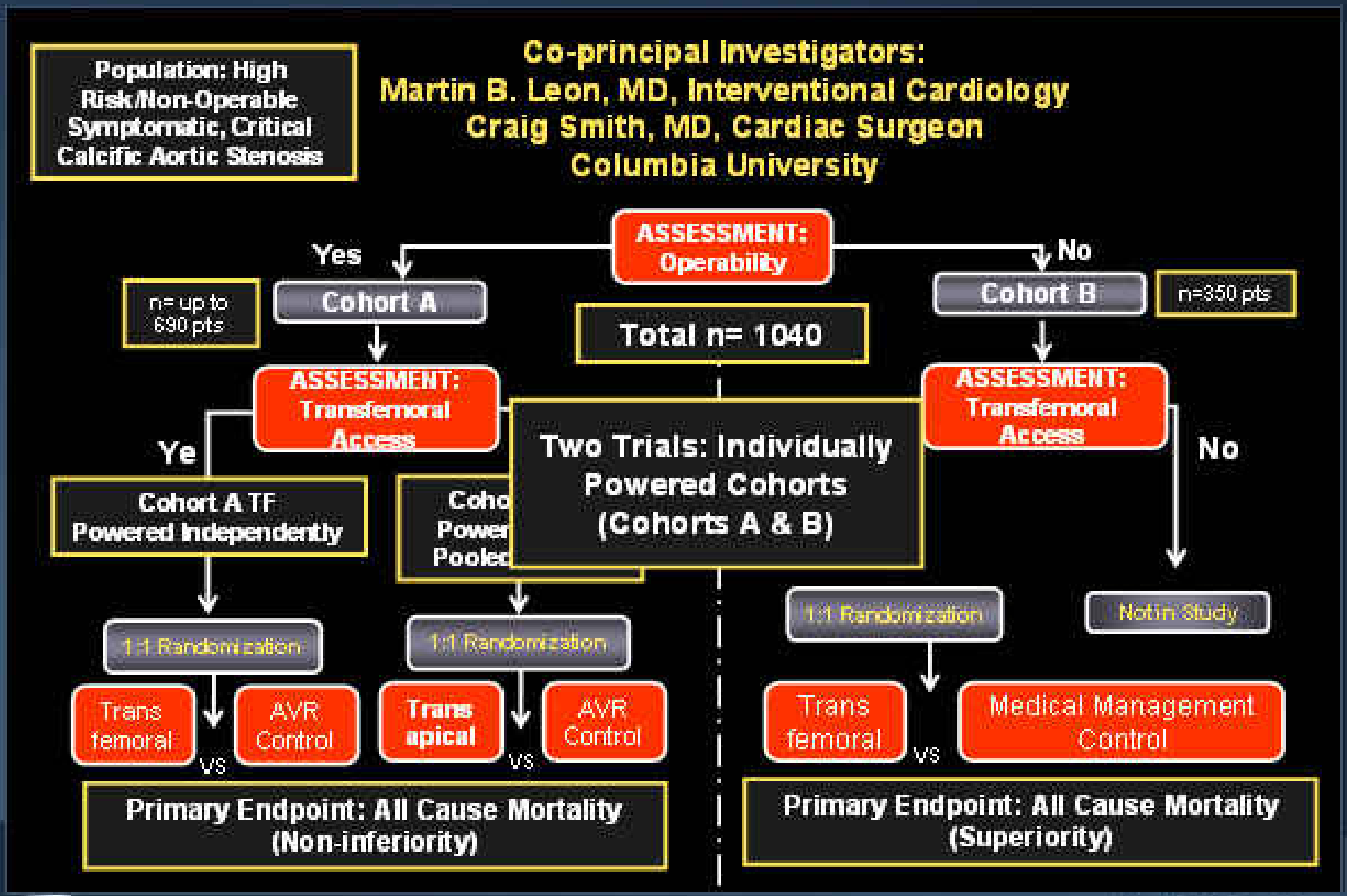
TAVR: Clinical Outcomes

What We Need to Know…

- Long-term rates and platform durability (late valve failure and late integrity of platform → clinical consequences)
- Late clinical complications – impact of multidetector peri-valvular a/i, effect on coronaries (disease progression, risk of CAD, MI, dysfunction, etc.
- Relative value and preference of trans-apical /s. trans-femoral (/s. other) approaches

- **Comparison vs. surgical AVR in high risk patients and vs. best current therapy in non-operable patients (PARTNER patient cohorts)**

The PARTNER IDE Trial



PARTNER Cumulative Enrollment
April, 2007 to September, 2008

As of February 1, 2009 … 700 patients enrolled

CARDIOVASCULAR RESEARCH FOUNDATION

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian

TAVR: Clinical Outcomes

What We Need to Know…

- **Differences among TAVR devices – trade-offs AND impact of next generation devices**

Future Aortic Valve Concepts

New TAVR Designs…

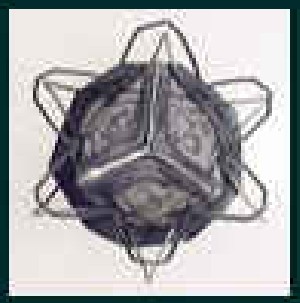
- Direct Flow
- Sadra
- AorTx
- Jena Valve
- HLT
- ABPS PercValve
- EndoTech
- Ventor Embracer











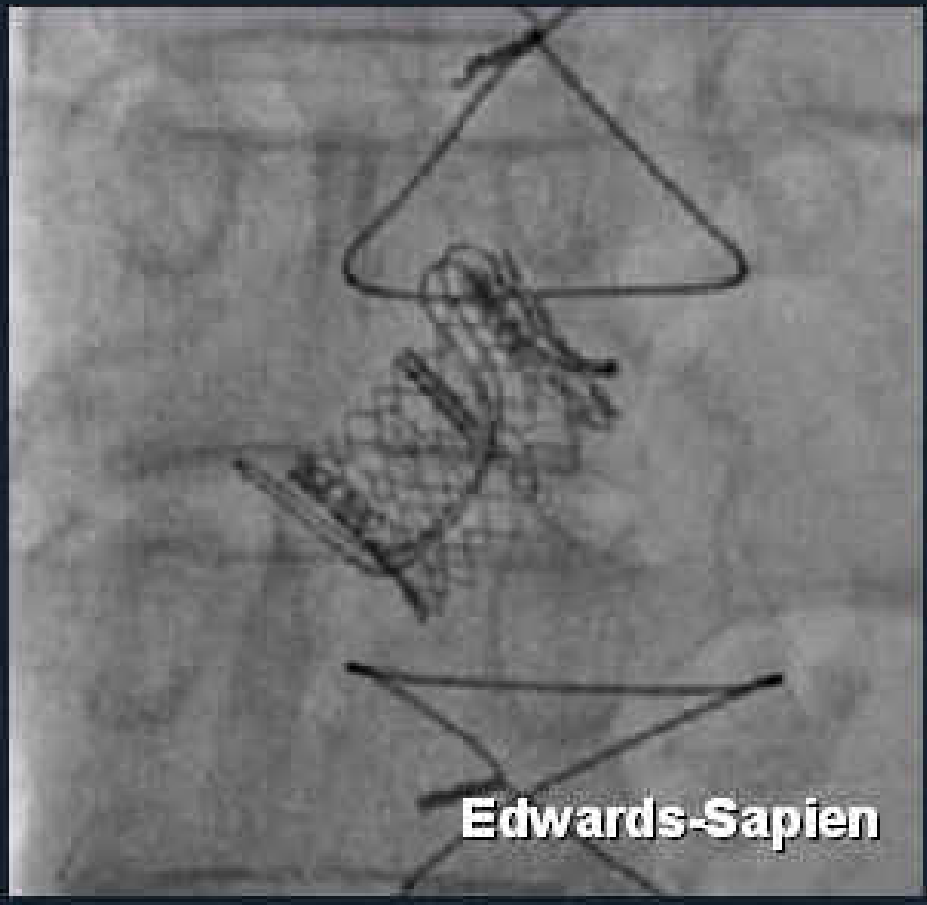
TAVR: Clinical Outcomes

What We Need to Know…

- Differences among 1st gen devices = trade-offs; 2nd gen devices
- **Comparison vs. surgical AVR in other patient cohorts (valve-in-valve, lower risk patients, AS + CAD, others)**

Transcatheter Valve Replacement
Endless Possibilities!

Trans-femoral Valve-In-Valve AVR

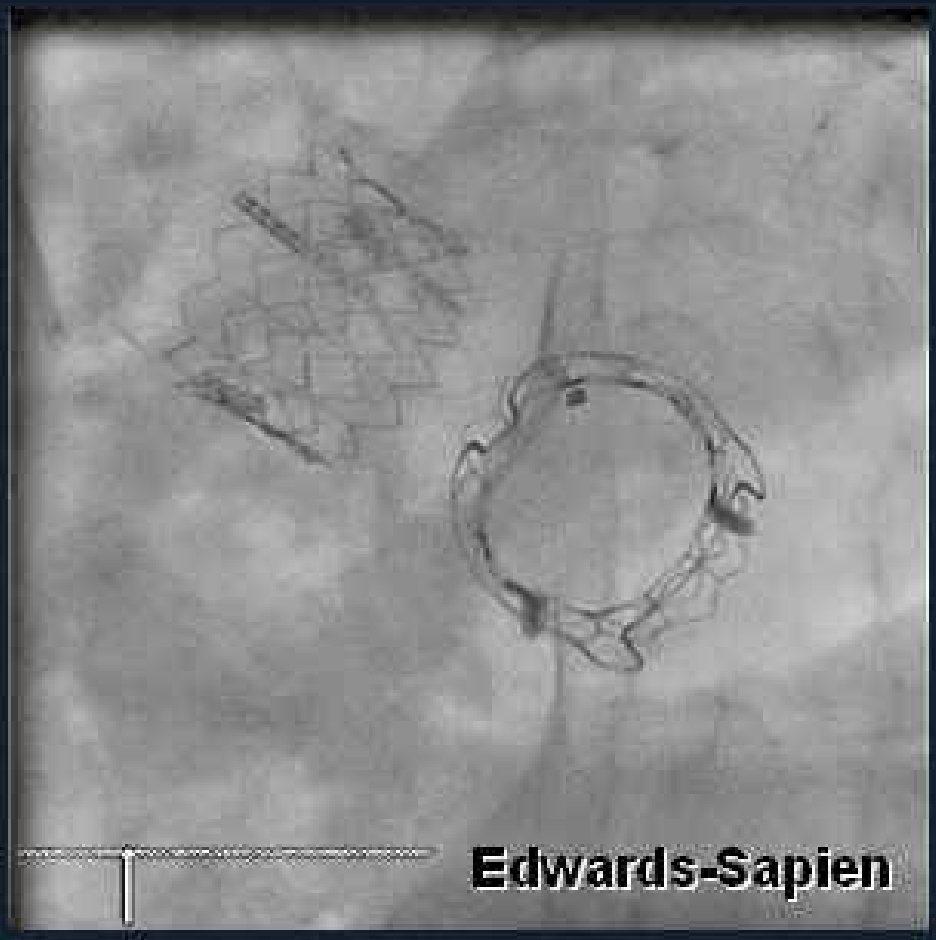


Courtesy of Dr. John Webb

Transcatheter Valve Replacement
Endless Possibilities!

Trans-apical AVR

Trans-apical MVR (valve-in-valve)



Courtesy of Dr. John Webb

TAVR: Clinical Outcomes

What We Need to Know…

- Differences among TA/Tr devices – trade-offs and impact of next generation devices
- Comparison vs. surgical AVR in other patient cohorts (val re-intervalve, lower risk patients, AS + CAD, others)
- **"Globalization" of TAVR – physician training concerns, surgeon vs. interventional operators, ? restricted access to valve experts, milieu issues (hybrid cath lab/ORs)**

Transcatheter AVR

Hybrid OR-Cath Lab

A unique collaborative experience!

TAVR: Clinical Outcomes

What We Need to Know…

- Differences among TAVR devices – trade-offs and impact of next generation devices
- Comparison vs. surgical AVR in other patient cohorts (valve-in-valve, lower risk patients, AS + CAD, others)
- “Globalization” of TAVR – physician training concerns, surgeon vs. interventional operators, ? restricted access to valve experts, milieu issues (hybrid cath lab/ORs)
- **Cost-effectiveness assessments and future reimbursement considerations - will have critical impact on future utilization!**

Transcatheter AVR

Summary Thoughts…

- TAVR devices and procedures have rapidly evolved with improved ease-of-use and generalizability to well-trained interventionalists everywhere!
- ***Ongoing pivotal RCTs (PARTNER) will provide the evidence-based medicine verification that TAVR is superior or comparable to surgery in non-operable and other high risk clinical scenarios.***
- Valve + platform ***durability*** still must be conclusively demonstrated (getting closer)!
- Once durability is established, we can expand clinical trials and indications for TAVR to most (not all) patients with severe AS!

Is Transcatheter AVR the *Standard of Care* for *High Risk* AS Patients?

Not until more "high quality" data is available with longer FU…

Transcatheter AVR

My Rosey Prophecy

Transcatheter AVR

Rules of Engagement