

Therapy in Evolution: Percutaneous Aortic Valve Replacement

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ANGIOPLASTY SUMMIT

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TRANSAPERTURE CARDIOVASCULAR THERAPEUTICS ASIA/PACIFIC

**Presenter Disclosure Information for
TCTAP 2010; April 27-30, 2010**

Martin B. Leon, M.D.

NON-PAID Consultant:
Edwards Lifesciences, Medtronic

Transcatheter AVI (TAVI)

Predicting the Future



**TAVI is the
MOST EXCITING
new procedure in the
field of interventional
cardiovascular
therapeutics!!!**

TAVI in Evolution

Exciting, “Breakthrough Technology...Why?”

- ***It’s FUN!!!***
 - requires advanced skills, discipline, and creativity
- ***It’s a multi-disciplinary playground***
 - finally a “unifying” procedure which embraces surgical involvement
- ***It’s incredibly fulfilling***
 - patient benefits are dramatic
- ***It’s an opportunity to transform a therapy for a common disease and help patients!***

Dr. Alain Cribier

First-in-Man PIONEER



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

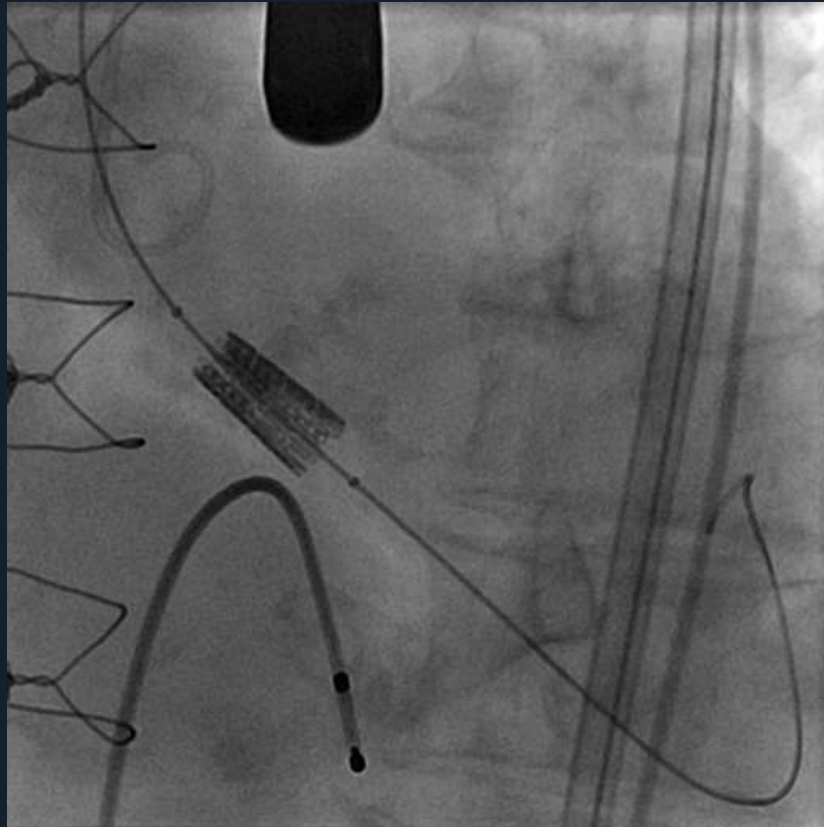
First Human Case Description

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

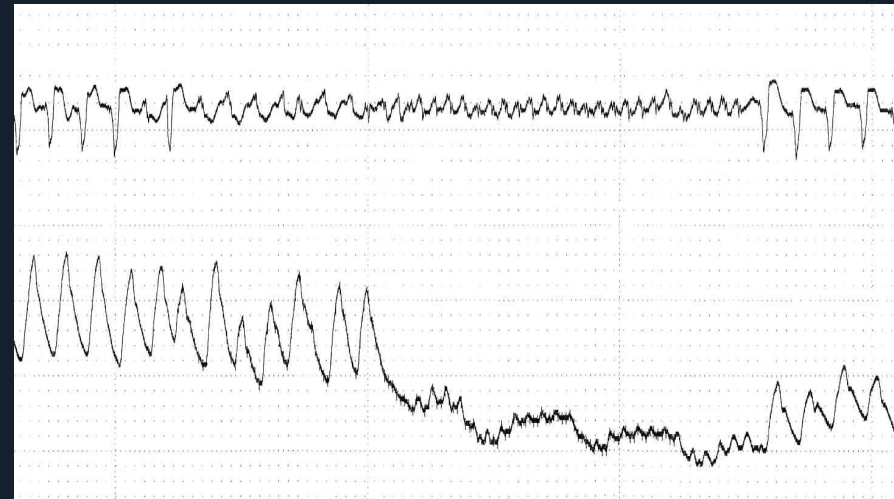
Conclusions— *Nonsurgical implantation of a prosthetic heart valve can be successfully achieved with immediate and midterm hemodynamic and clinical improvement.*

April 16, 2002

Retrograde Trans-femoral Edwards Aortic Valve Deployment



Rapid pacing : 220/min



TAVI in Evolution

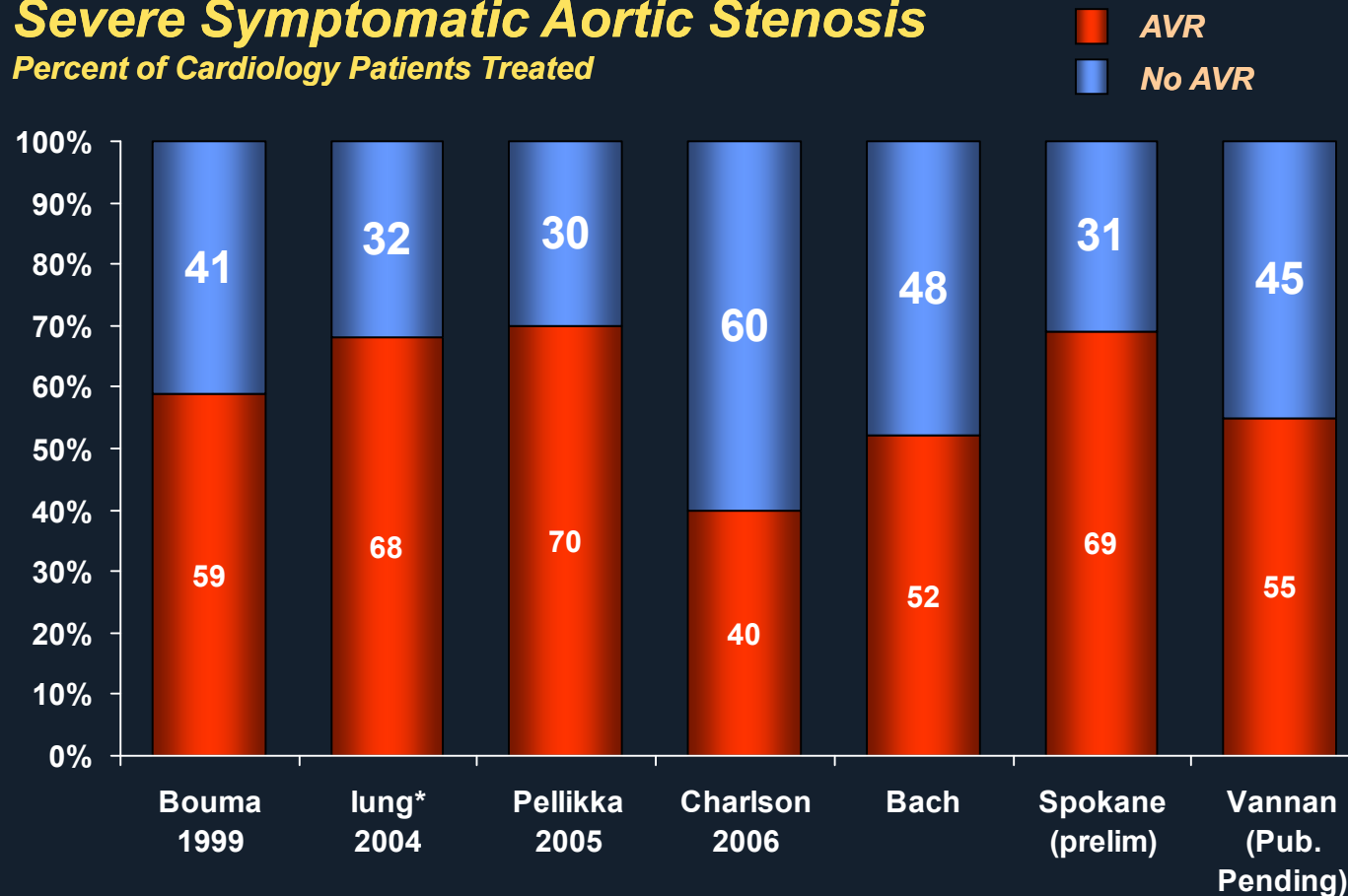
Lessons Learned...

- 1. The “high risk” severe AS patients are “under-treated” and are excellent candidates for TAVI procedures***
 - Patient screening and case selection for TAVI is demanding and is critical to achieve optimal outcomes**

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

Severe Symptomatic Aortic Stenosis

Percent of Cardiology Patients Treated



Under-treatment especially prevalent among patients managed by Primary Care physicians

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. lung 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

TAVR Patient Selection

Includes Careful Frailty Assessment

Patient A



vs.

Patient B



Same age and predicted risk
One passes the “eyeball test” – one does not

***Frailty is being studied systematically as part of
the PARTNER U.S. IDE study***

TAVI in Evolution

Lessons Learned...

2. Multiple technology platforms have achieved excellent prosthetic valve hemodynamic results

- **Both acute and mid-term valve performance has surpassed expectations**
- **Equivalent to surgical valve implants**

TAVI Technologies

Current Generation Devices



Edwards Lifesciences



Medtronic CoreValve

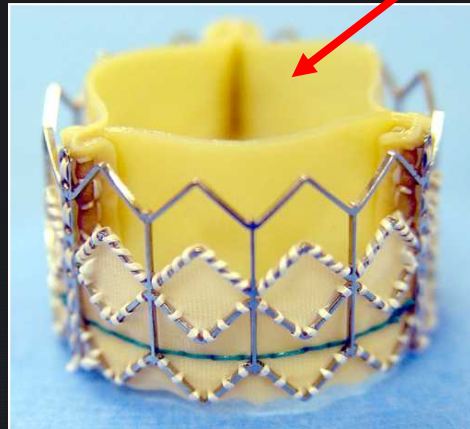
TAVI Technologies

Current Generation Devices

- **Edwards Aortic Bioprosthesis**
 - Balloon expandable stainless steel bioprosthesis
 - Equine → Bovine pericardial valve
 - Sheathed (RetroFlex) with tip deflection
 - Antegrade, retrograde, or trans-apical approach
- **CoreValve Revalving™ System**
 - Self-expanding nitinol cage bioprosthesis
 - Porcine pericardial valve
 - Sheathed system (low profile = 18 Fr)
 - Retrograde (femoral + subclavian) approach

The Current Generation

Edwards – SAPIEN THV

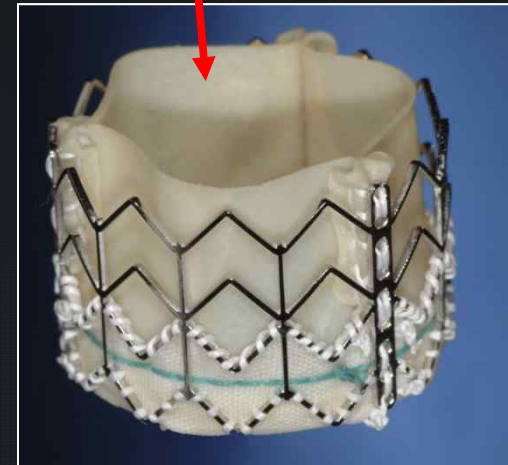


Bovine Tissue
ThermaFix Treatment
Pericardial Mapping
Leaflet Deflection
Proprietary Processing

New
Skirt Height

Edwards-SAPIEN THV

Untreated Equine
Tissue



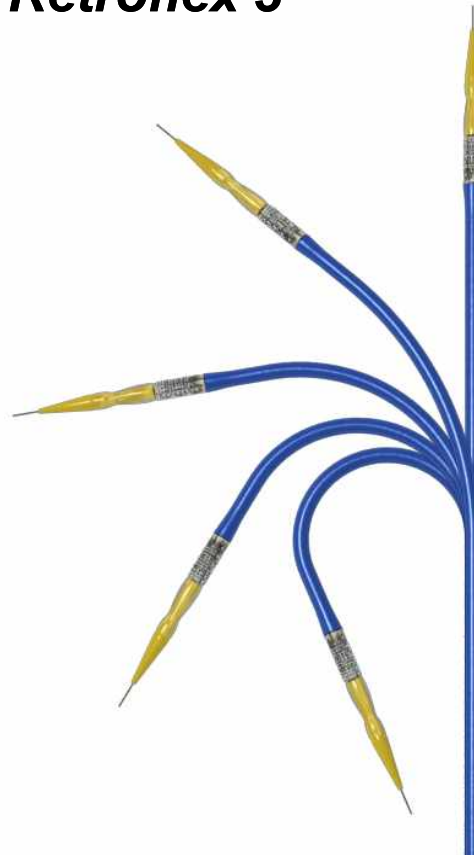
Current
Skirt Height

Cribier-Edwards THV

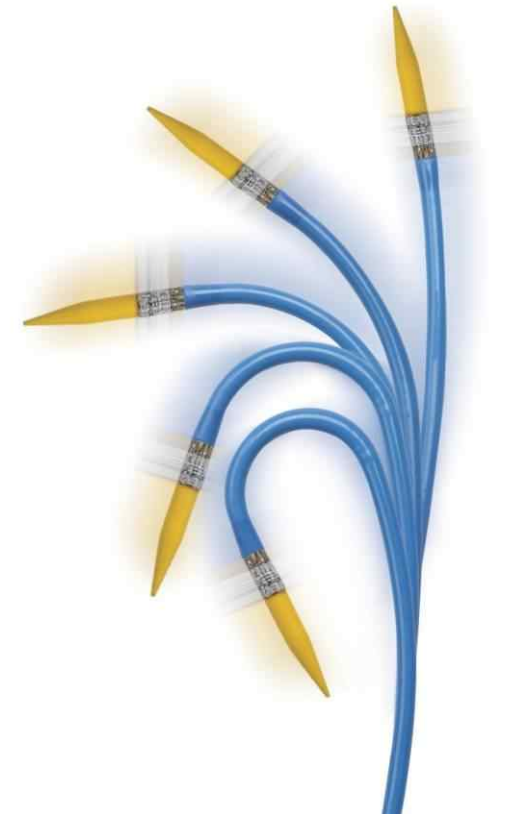
Edwards *Flex Cath* Delivery System Evolution



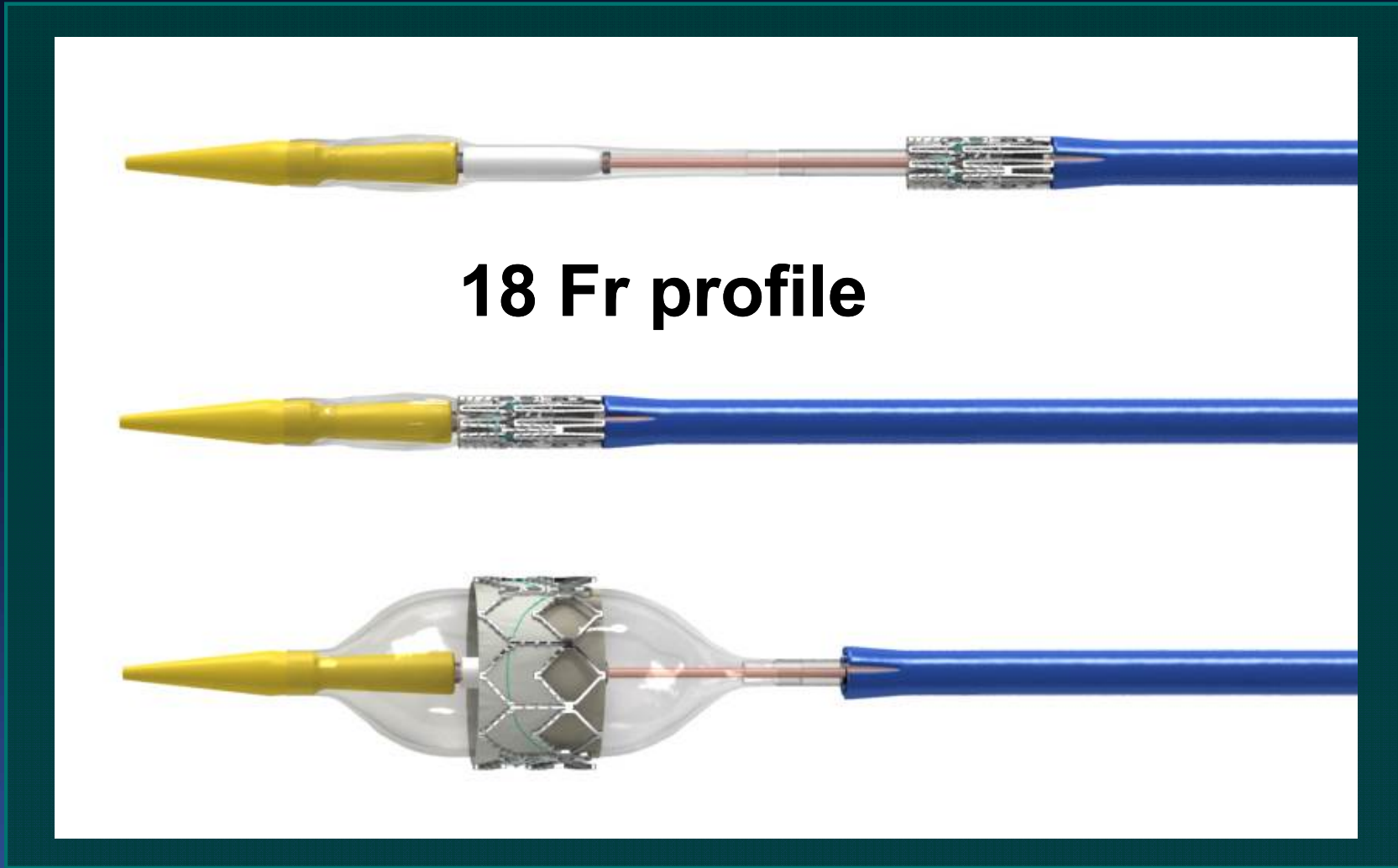
Retroflex 3



Retroflex 2

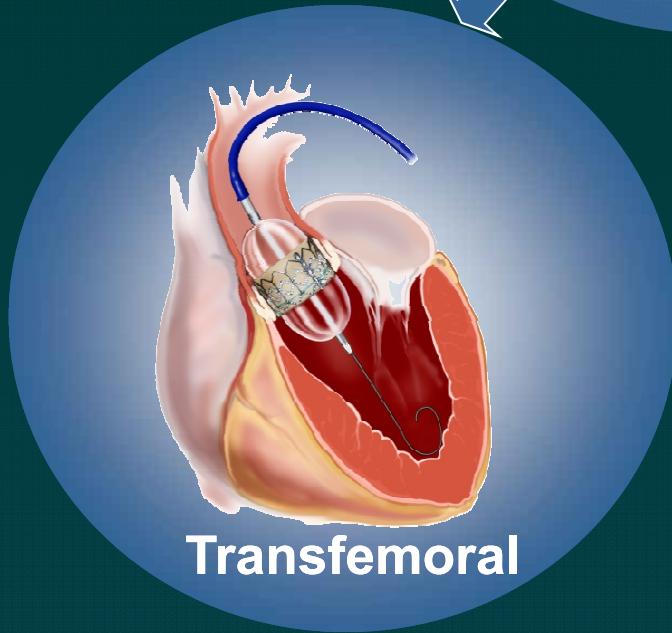
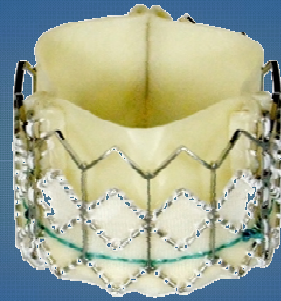


Sapien XT + NovaFlex Delivery System

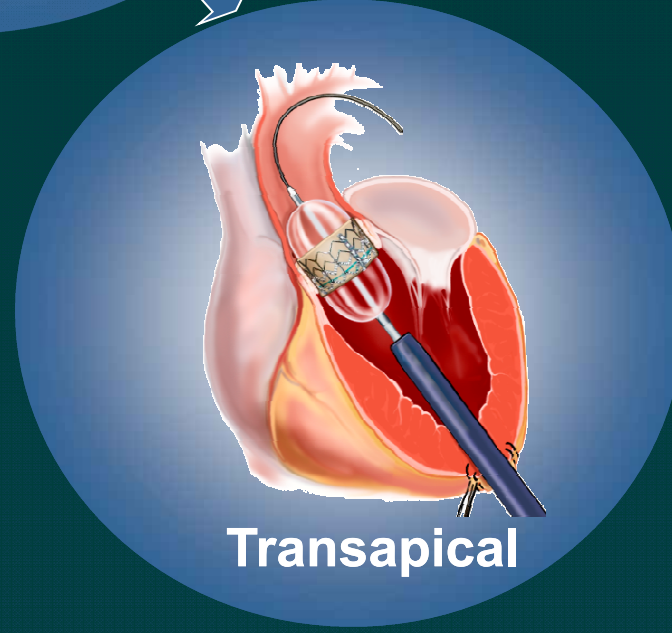


Transcatheter AVI

Transapical Access Route



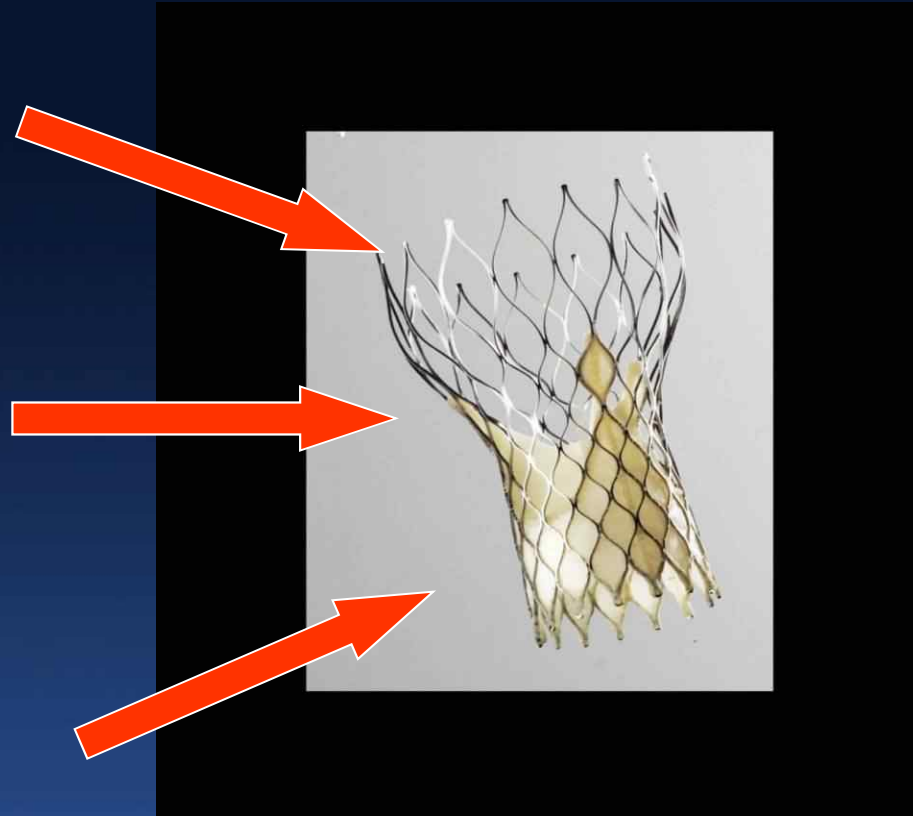
Transfemoral



Transapical

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

CoreValve **ReValving** System *Delivery Catheter Evolution*

GEN1
8mm



GEN2
7mm



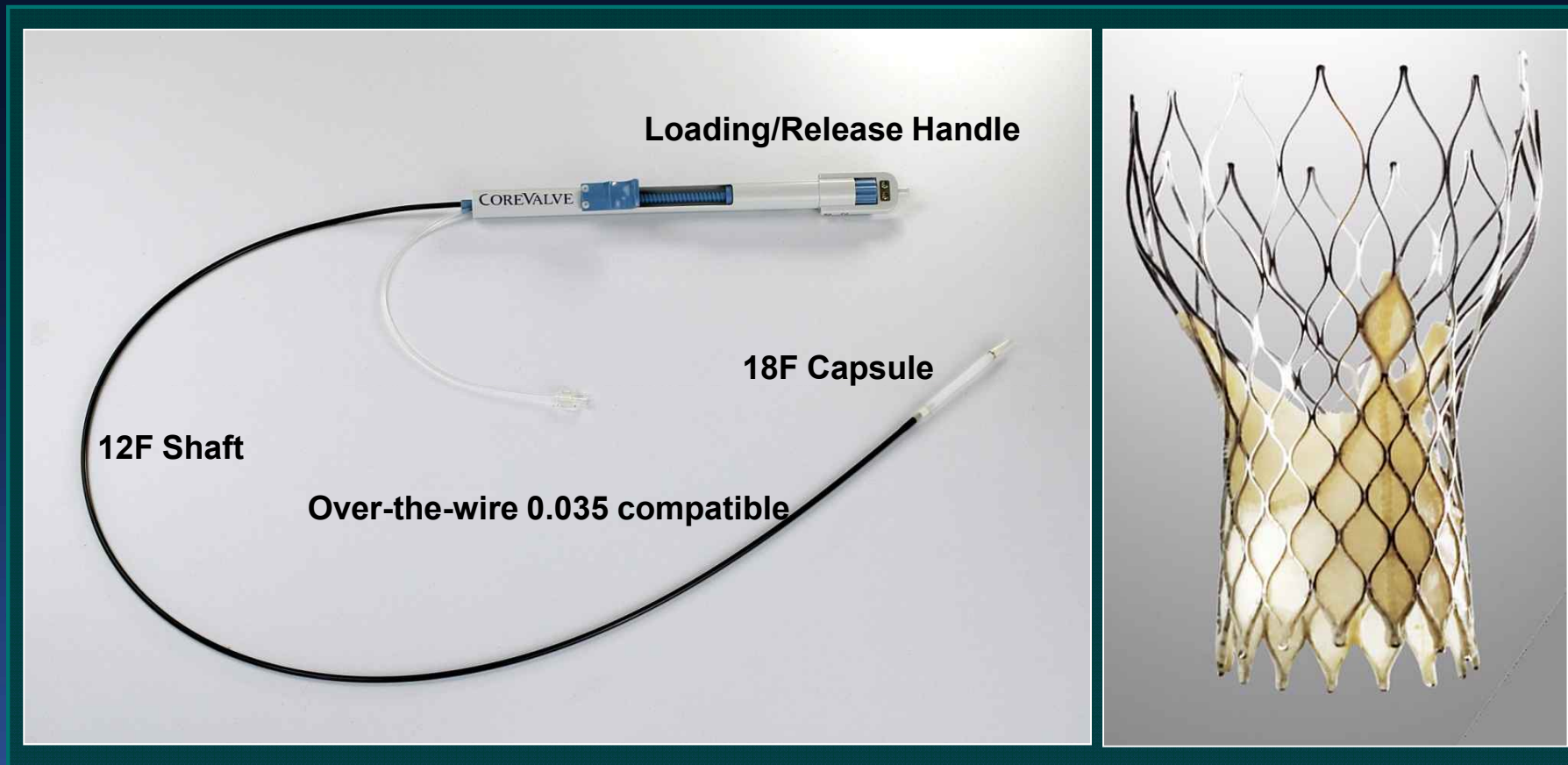
GEN3
6mm
(18 Fr)



12 Fr shaft

CoreValve ReValving™ System

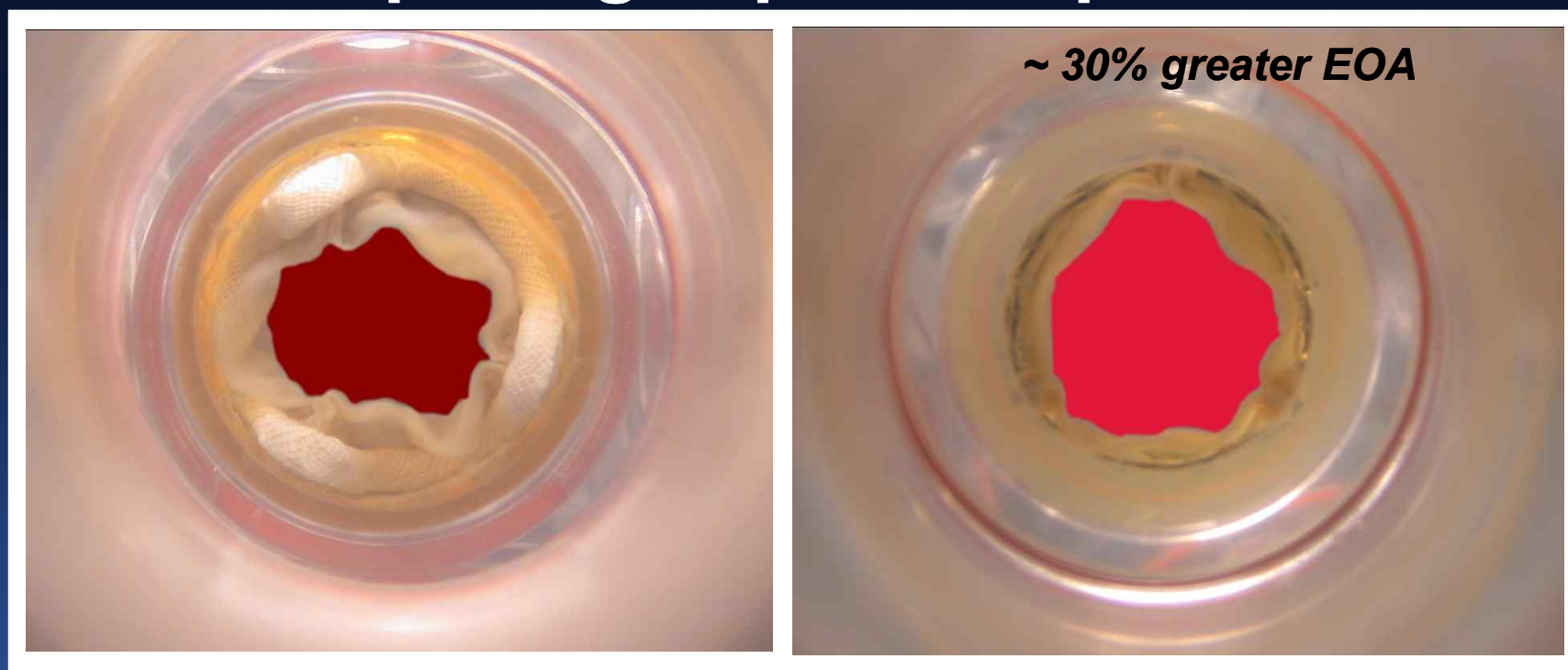
18 Fr Delivery System



Cribier-Edwards Aortic Bioprosthesis

Hemodynamic Tests

Effective Orifice Area:
Full opening in pulse duplicator

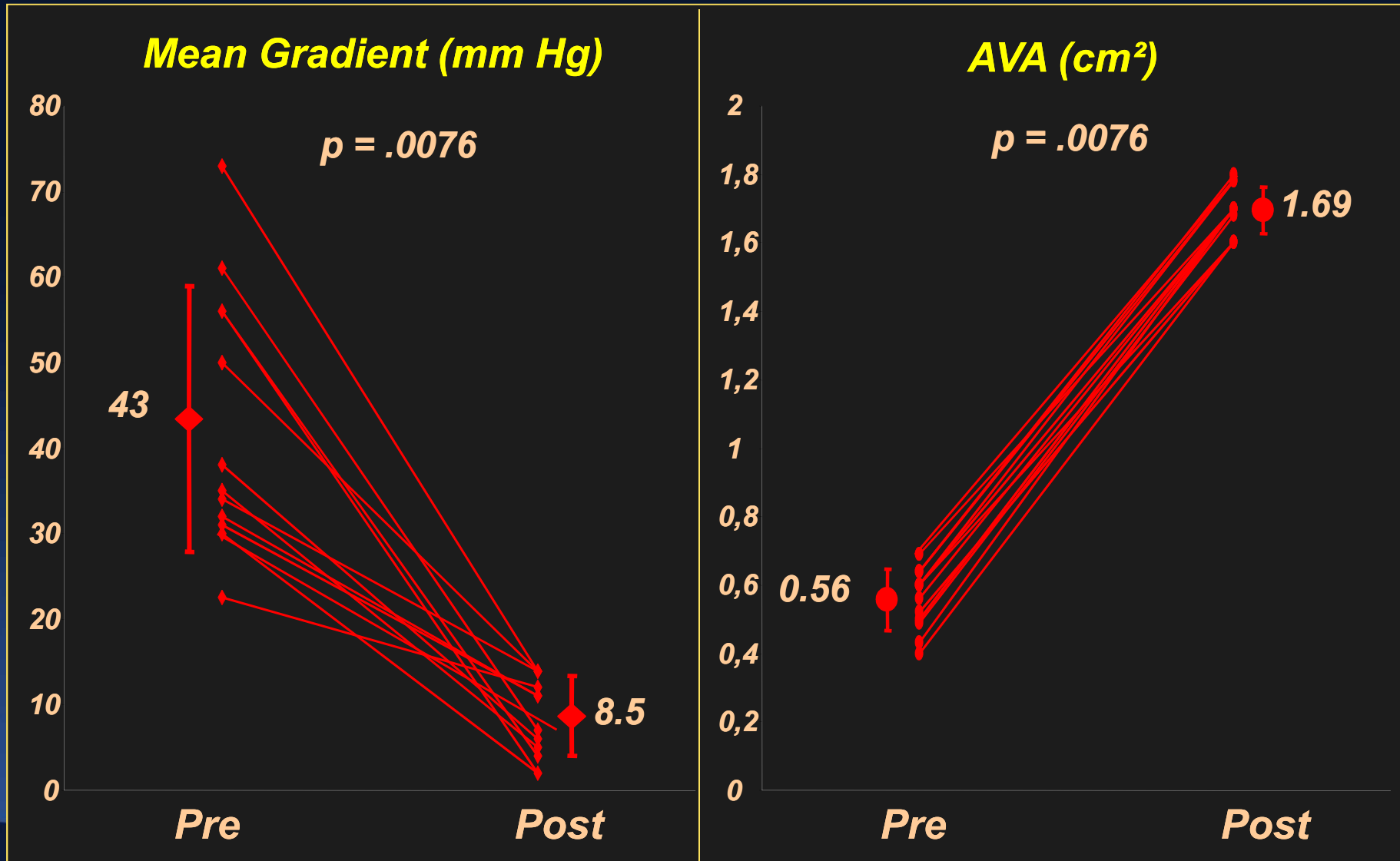


Hancock II - 23 mm

THV - 23mm

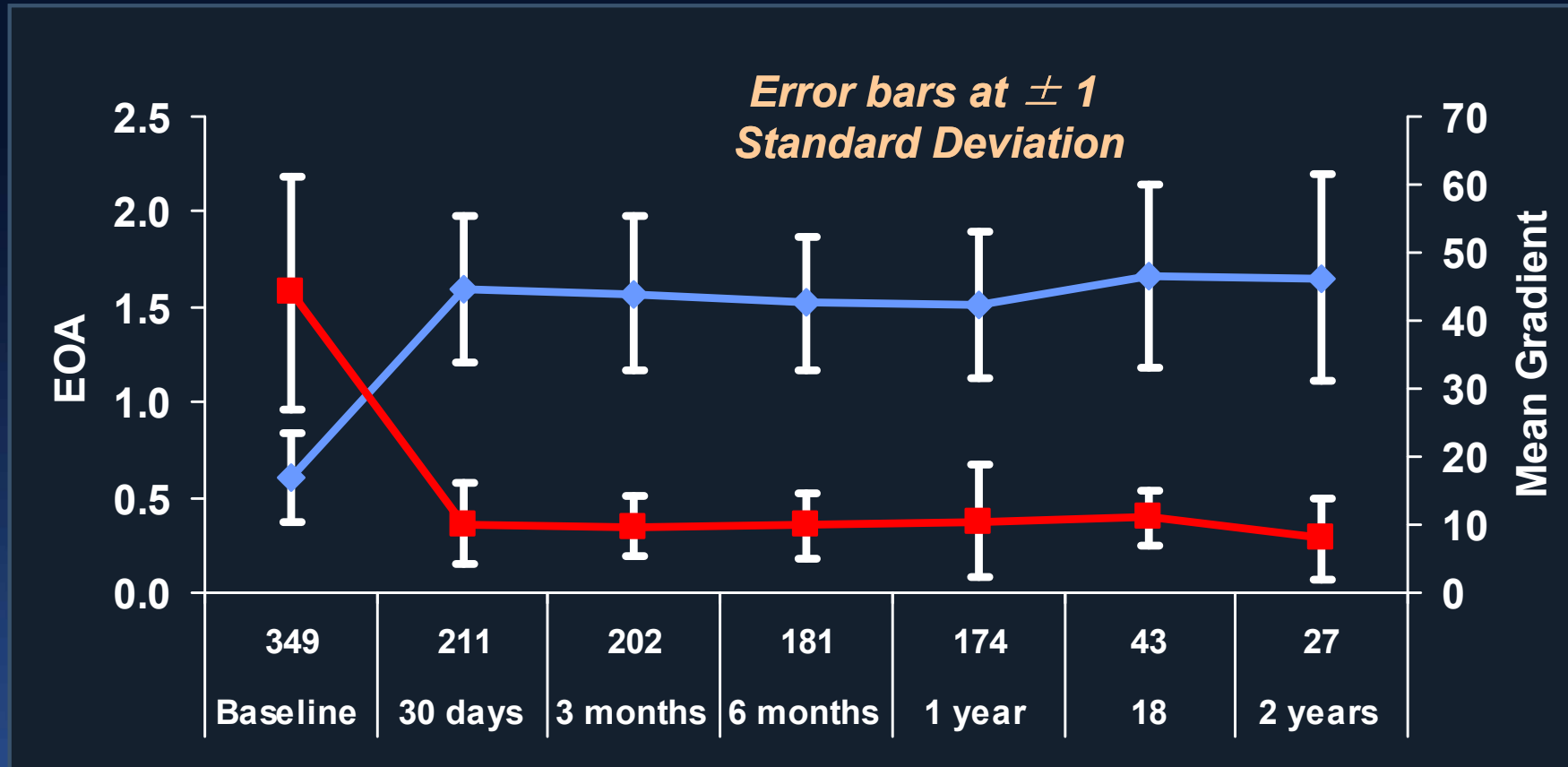
Cribier – Early PHV Experiences

Procedural Results (n=16)



POOLED* Monitored Edwards TAVI

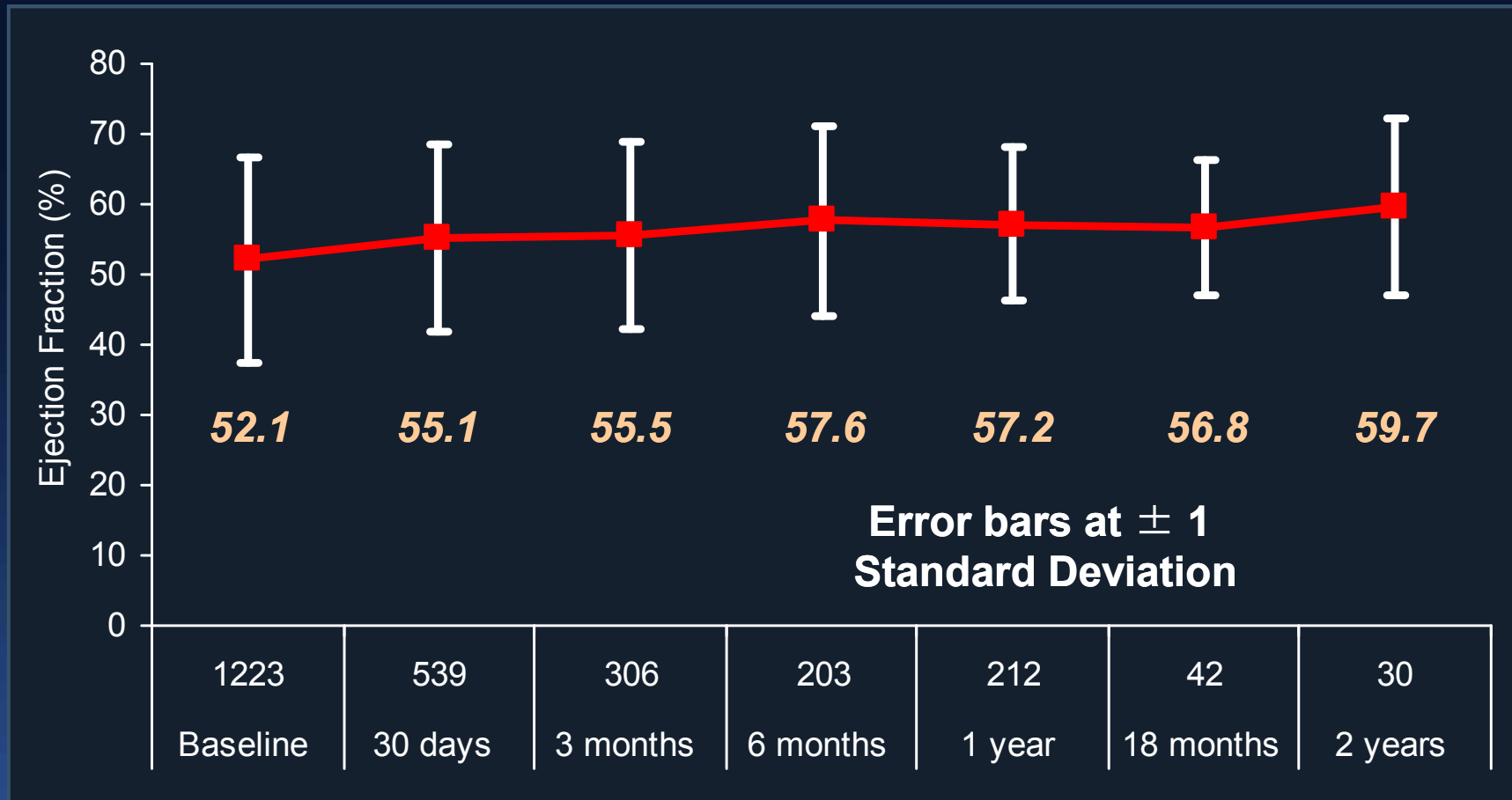
Mean Gradients and EOA (Echo)



** REVIVE, REVIVAL, TRAVERCE
and PARTNER EU*

POOLED* + SOURCE Edwards TAVI

LV Ejection Fraction (Echo)



*** REVIVE, REVIVAL, TRAVERCE
and PARTNER EU**

TAVI in Evolution

Lessons Learned...

3. Multiple technology platforms have also achieved acceptable early and mid-term clinical outcomes

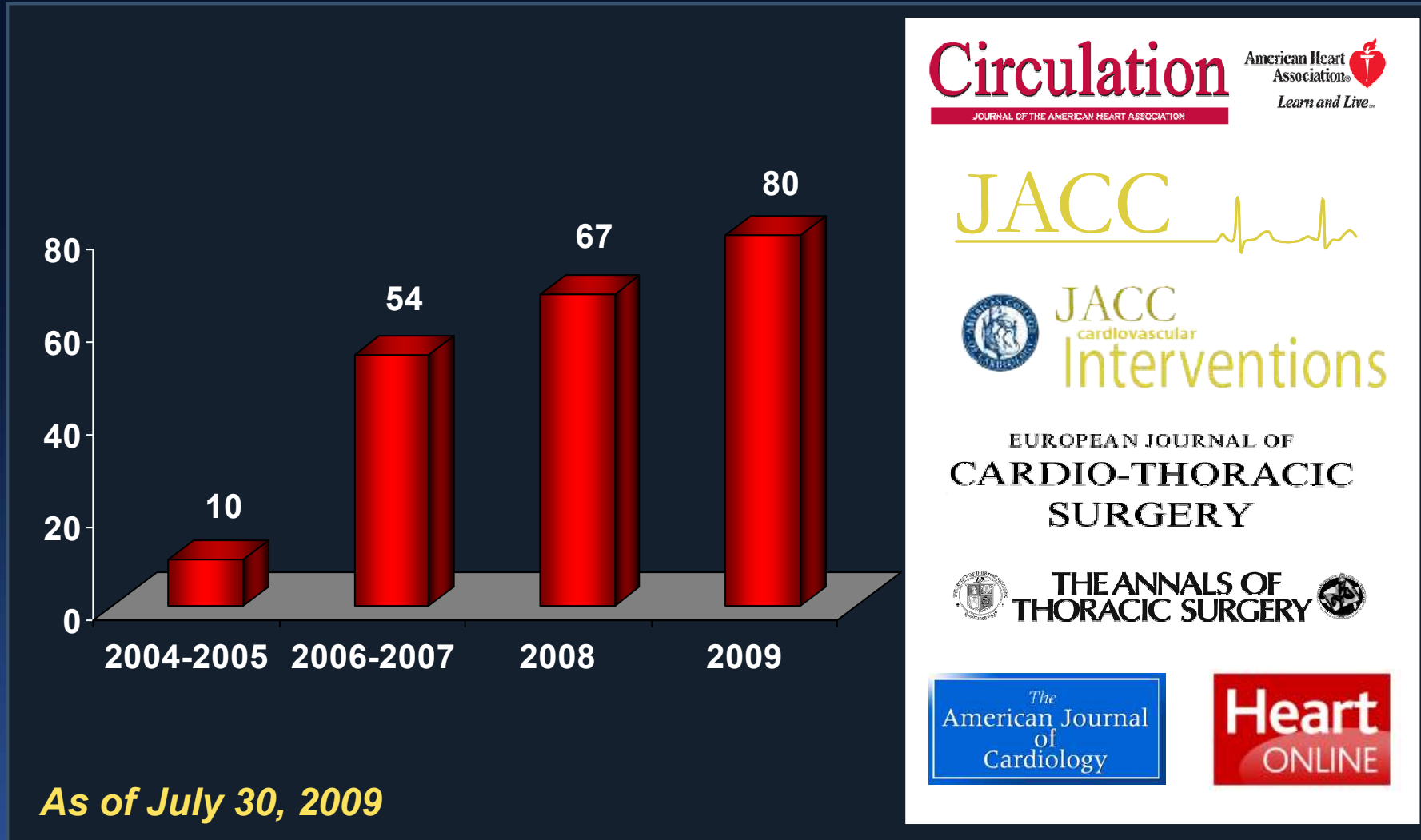
- **Clinical outcomes are improving, perhaps due to better patient selection, device and procedure enhancements, and “learning curve” issues**
- **Clinical benefit is remarkable, sustained, and very fulfilling!**
- **Clinical trial processes require standardization and increased rigor**

TAVI in Evolution

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, para-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!***

Edwards Lifesciences THV Publications



What is “VARC”?



- “VARC” is the *Valve Academic Research Consortium*, an attempt to harness positive ARC methodologies, but customize the process to the special needs of valvular heart disease therapies
- *GOAL: arrive at consensus on (1) essential endpoints and their definitions and (2) clinical trial methodology.*
- AROs = Cardialysis, CRF, HCRI and DCRI and the Societies represented = AATS, ACC, AHA, EACTS, ESC, SCAI, and STS
- First meeting in SF at TCT on September 19th 2009; second meeting in Amsterdam on December 5-6, 2009; manuscript in preparation

Edwards TAVI

Clinical Data Sources

Edwards

Other Studies

Transseptal Experience
(RECAST, I-REVIVE; 36 pts)

FIRST-in-MAN

VANCOUVER single center
(TF=164 pts, TA=86 pts)

REVIVE (OUS, TF)
TRAVERCE (OUS, TF)
REVIVAL (US, TF)

**OVERALL TOTAL
3726 PTS**

US single center
(TF=11 pts, TA=24 pts)

PARTNER EU (OUS, TF/TA 130 pts)
SOURCE (OUS, TF/TA, 1123 pts)

**POST
CE-APPROVAL**

CANADA multi-center (6)
(TF=167 pts, TA=172 pts)

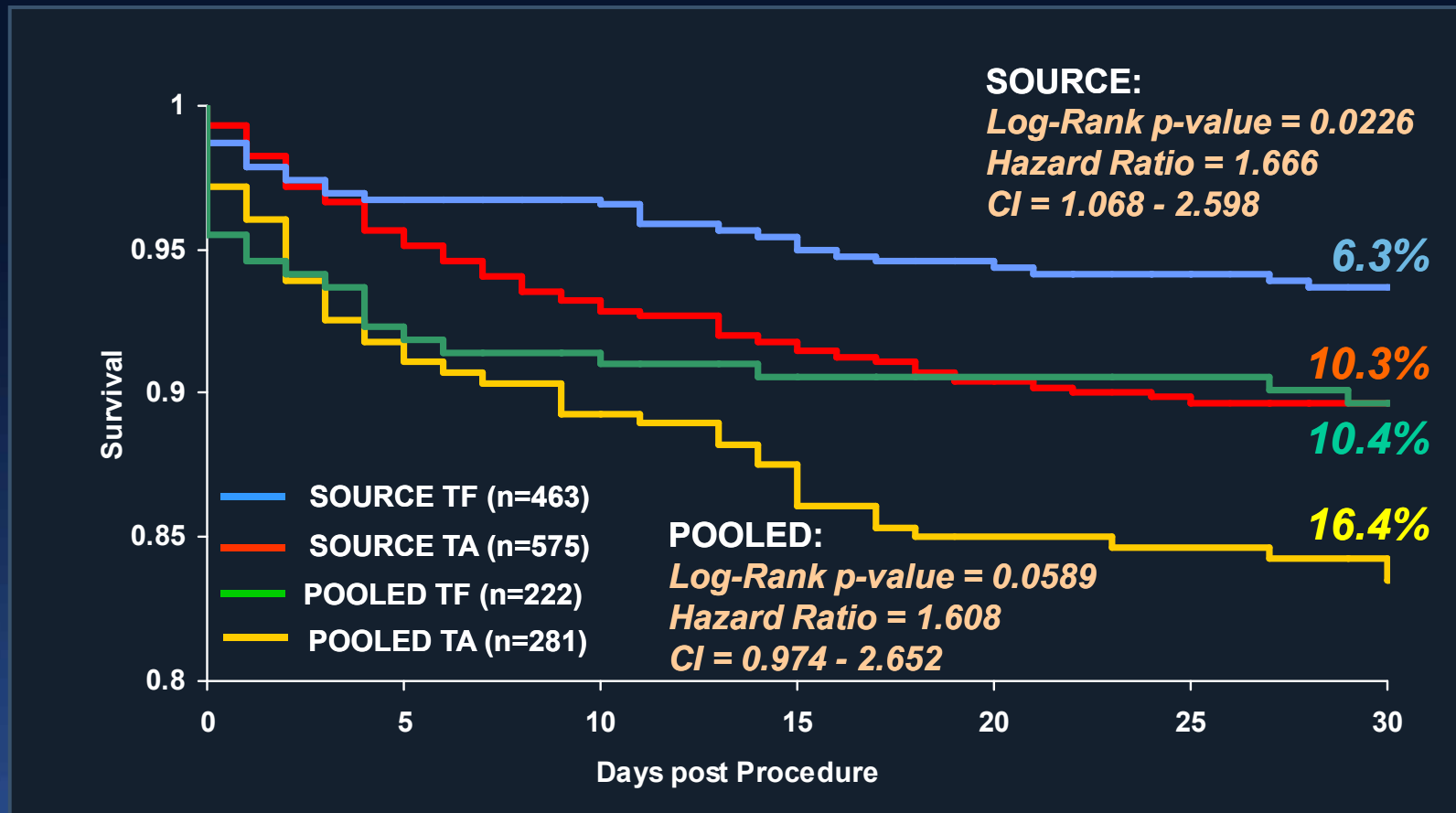
TOTAL = 664 PTS

PARTNER FDA
(US/OUS, TF/TA ~1400 pts)

PIVOTAL RCT

TOTAL = 3062 PTS

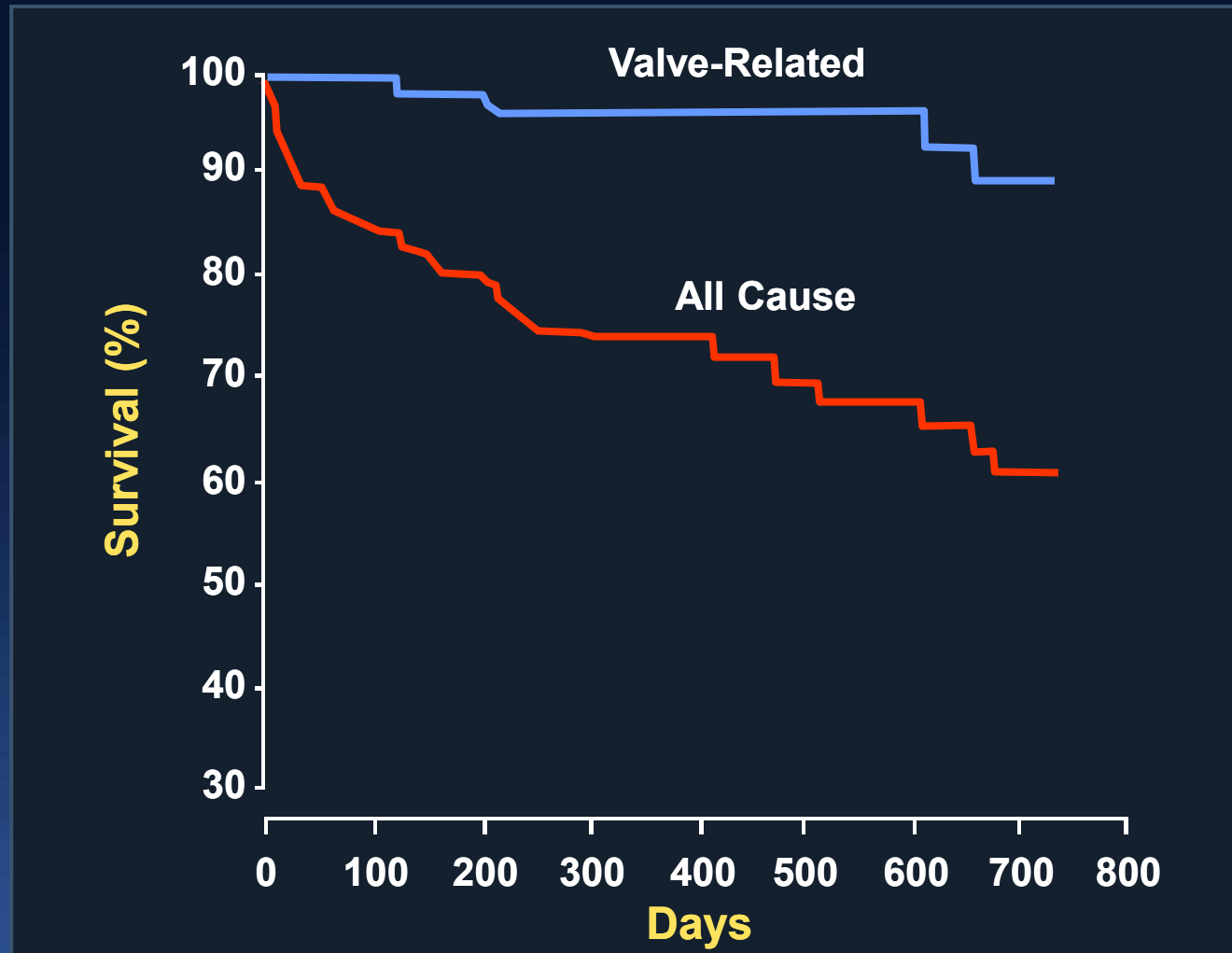
POOLED* Monitored Edwards TAVI 30-Day Mortality (vs. SOURCE)



* REVIVE, REVIVAL, TRAVERCE
and PARTNER EU

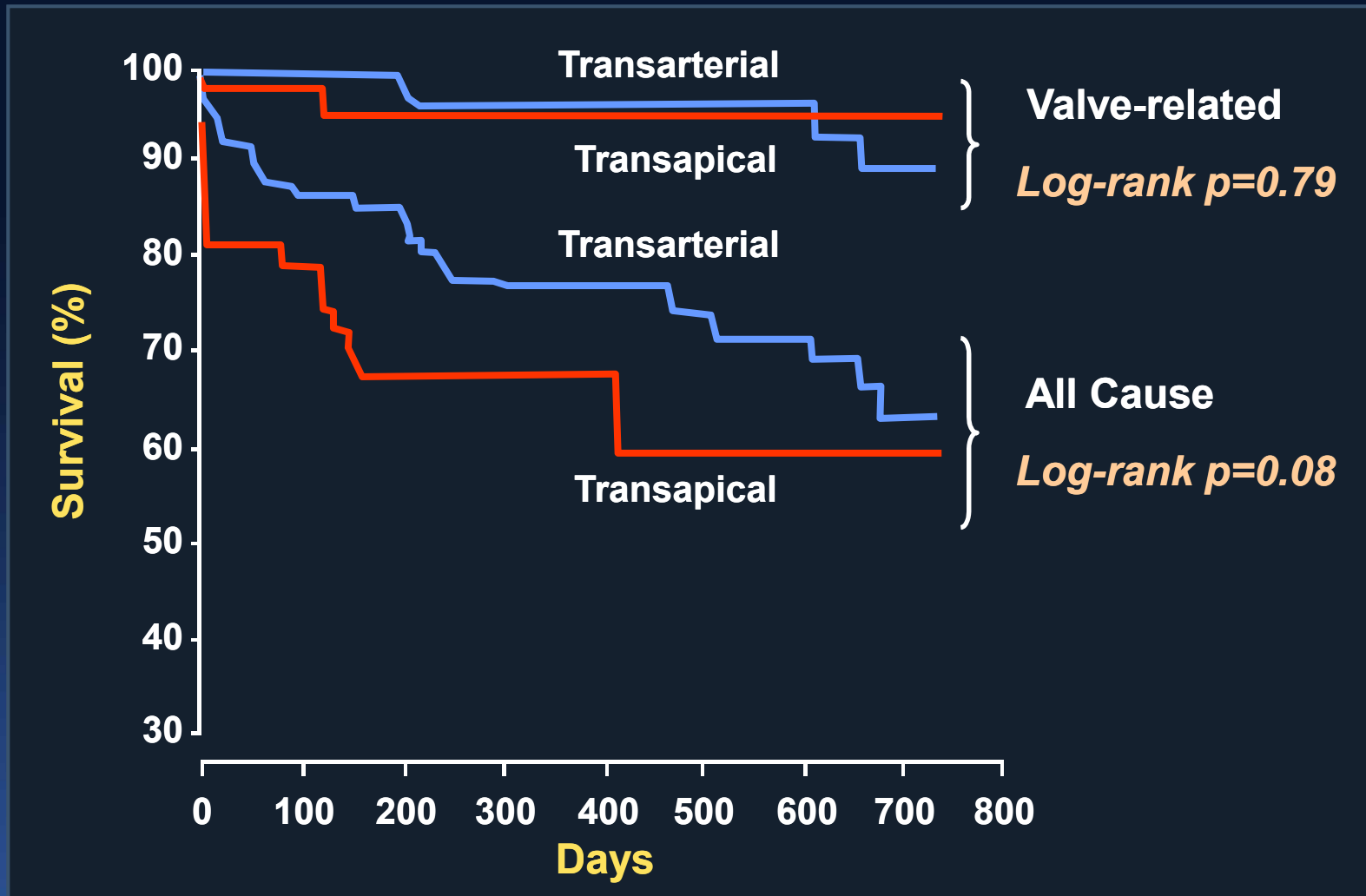
Vancouver TAVI Experience

Survival at 1 Year



Vancouver TAVI Experience

Survival at 1 Year



PARTNER EU Trial

Risk Profiles

TF (n=61)

TA (n=69)

Logistic EuroSCORE

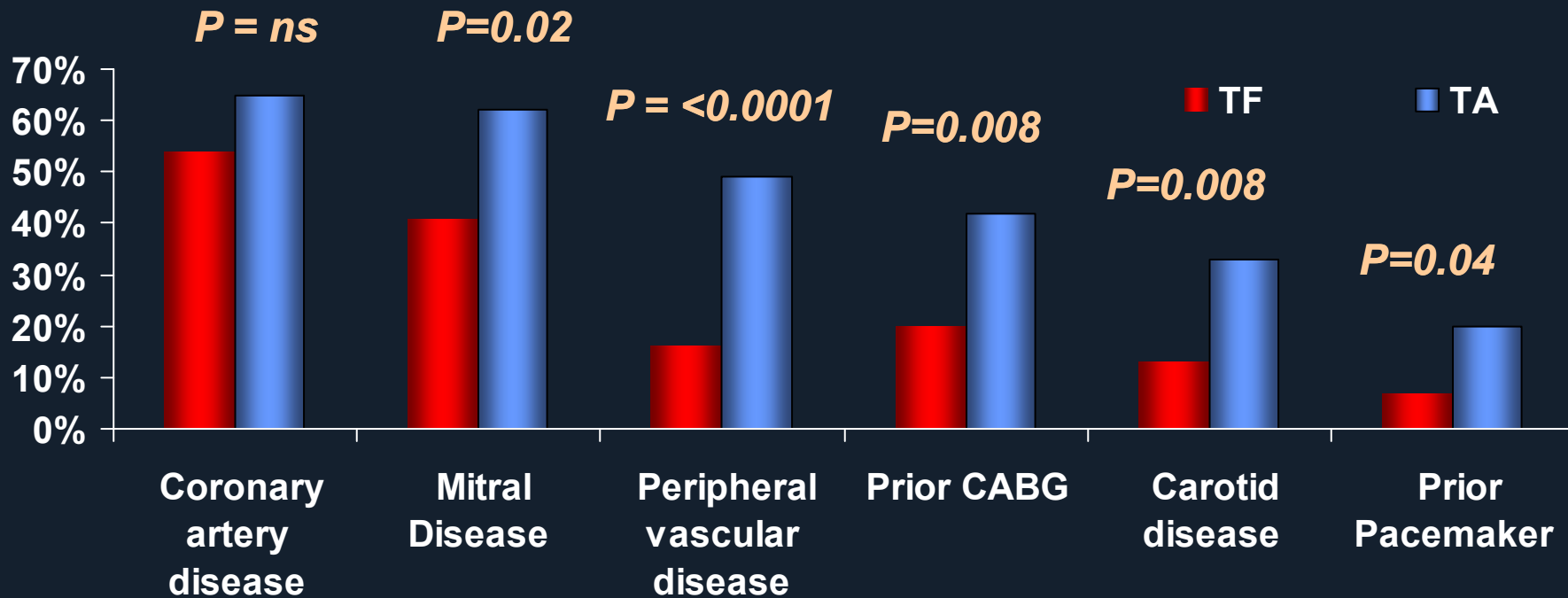
25.7 ± 11.5 (Range: 6-65)

33.8 ± 14.7 (Range: 5-72)

STS Score

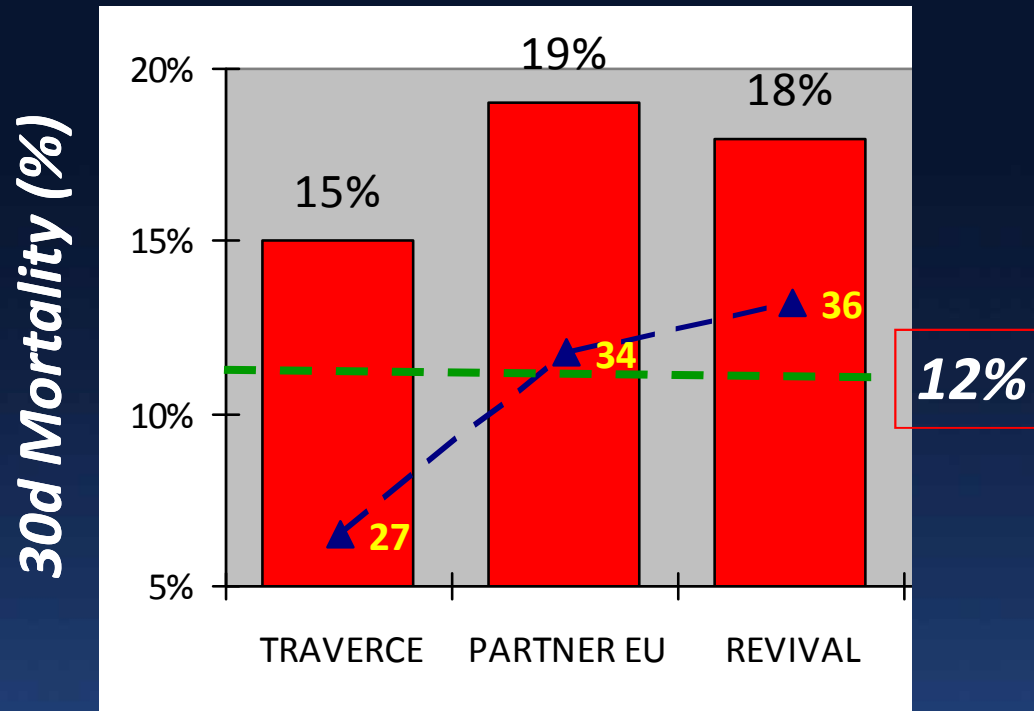
11.3 ± 6.1 (Range: 4-32)

11.8 ± 6.8 (Range: 2-41)



TAVI in Evolution

Trans-apical

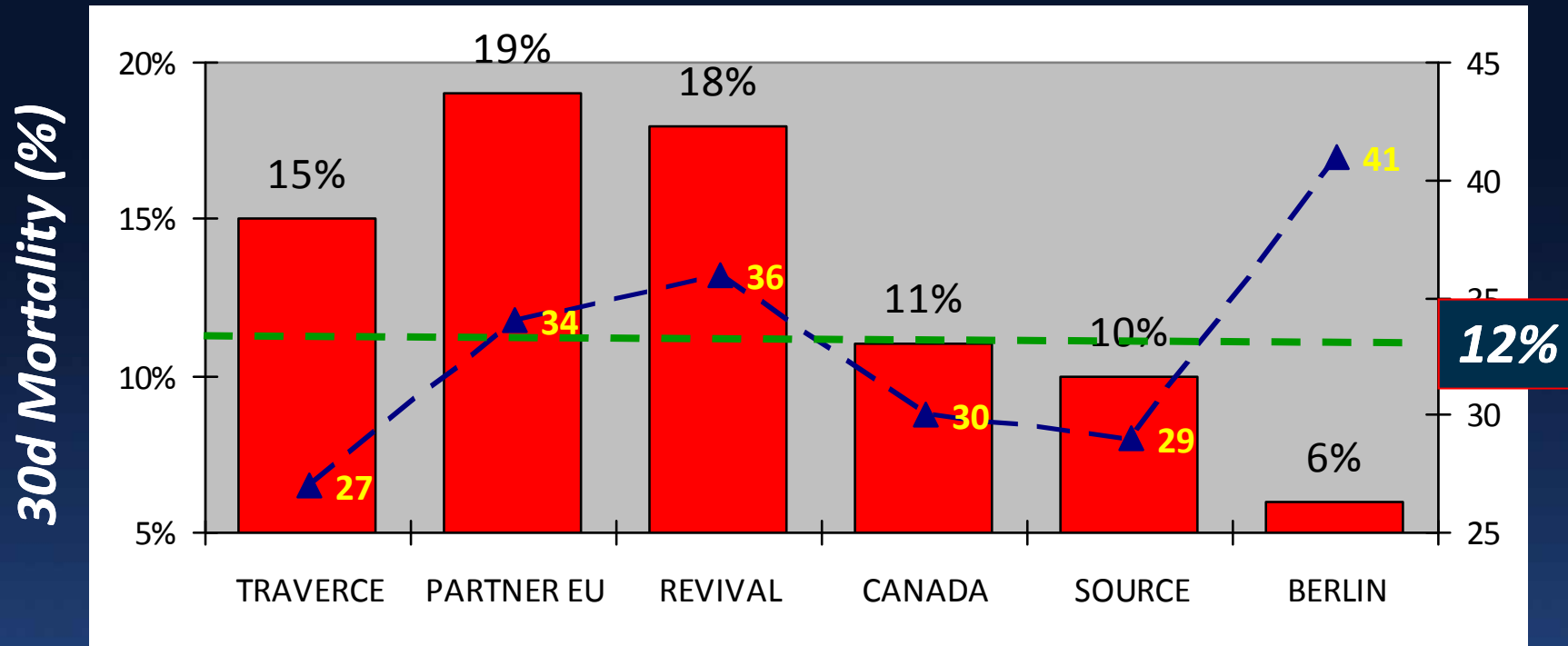


Clinical Trials

Improved short-term outcomes!

TAVI in Evolution

Trans-apical



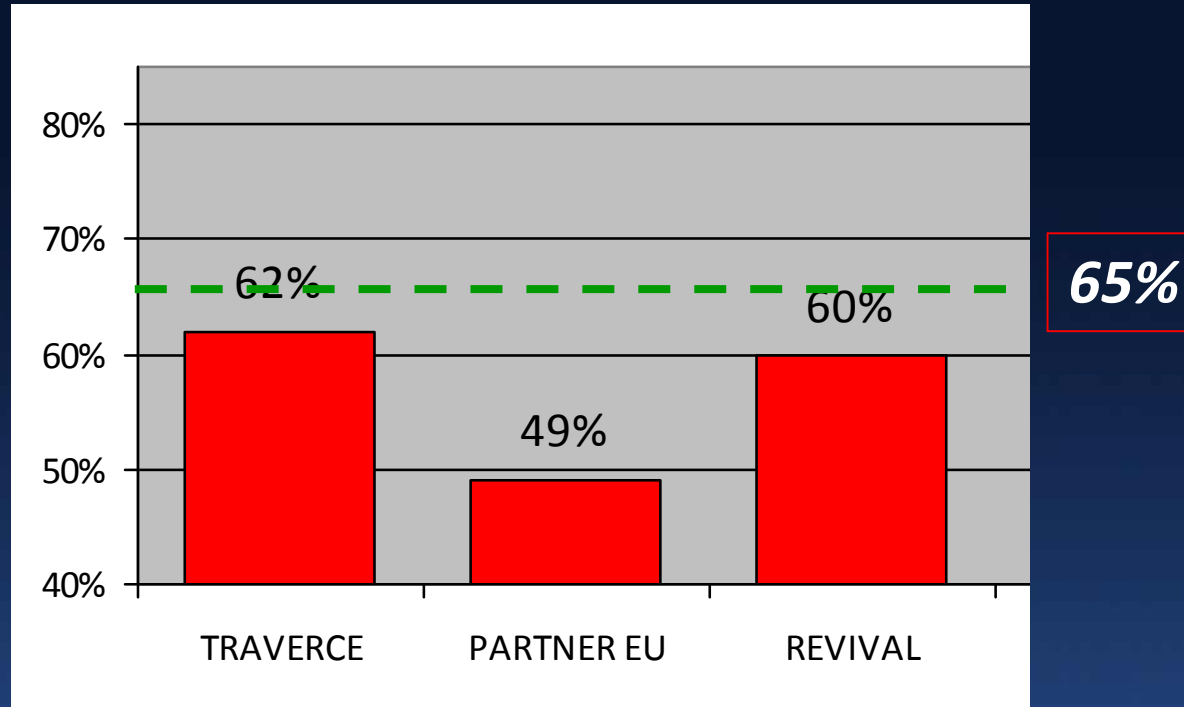
Clinical Trials

Improved short-term outcomes!

TAVI in Evolution

Trans-apical

1-year survival (%)



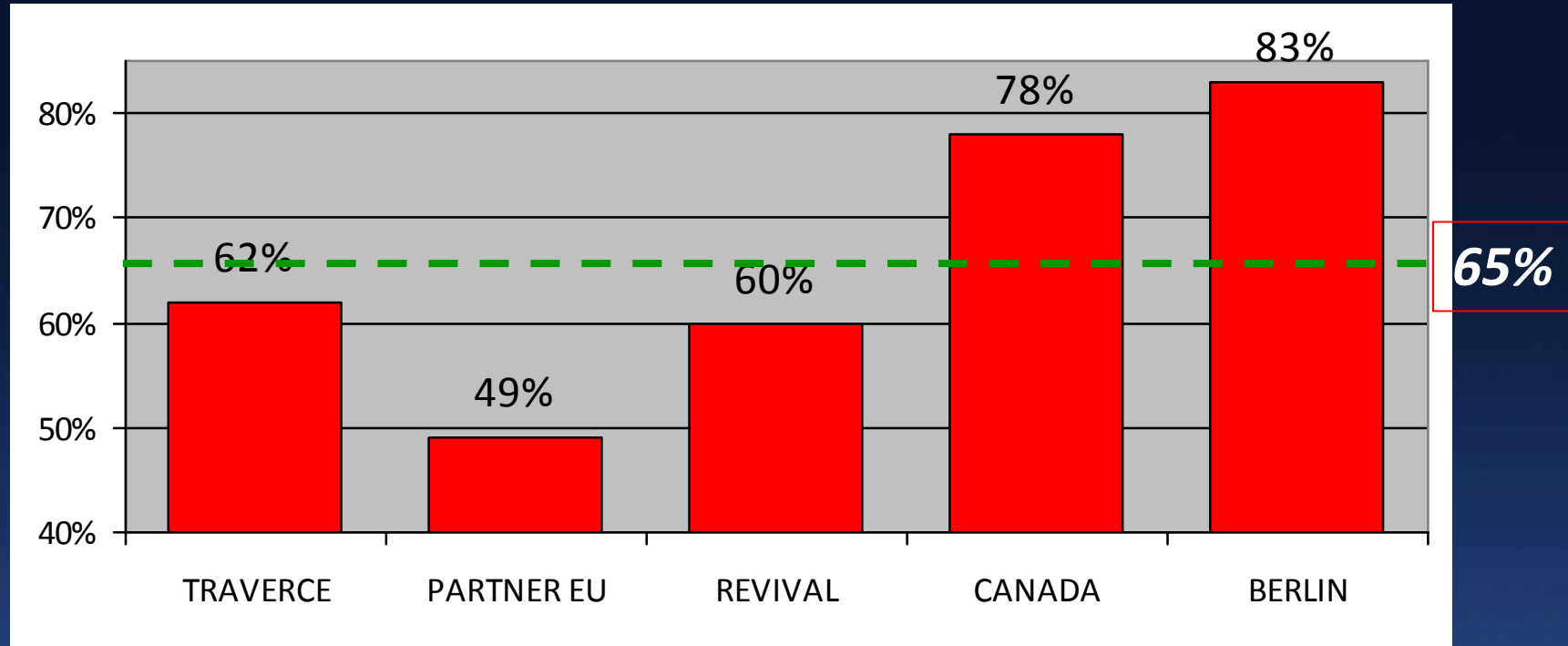
Clinical Trials

Improved one-year outcomes!

TAVI in Evolution

Trans-apical

1-year survival (%)



Clinical Trials

Improved one-year outcomes!

Edwards TAVI

Predictors of 30-Day Mortality

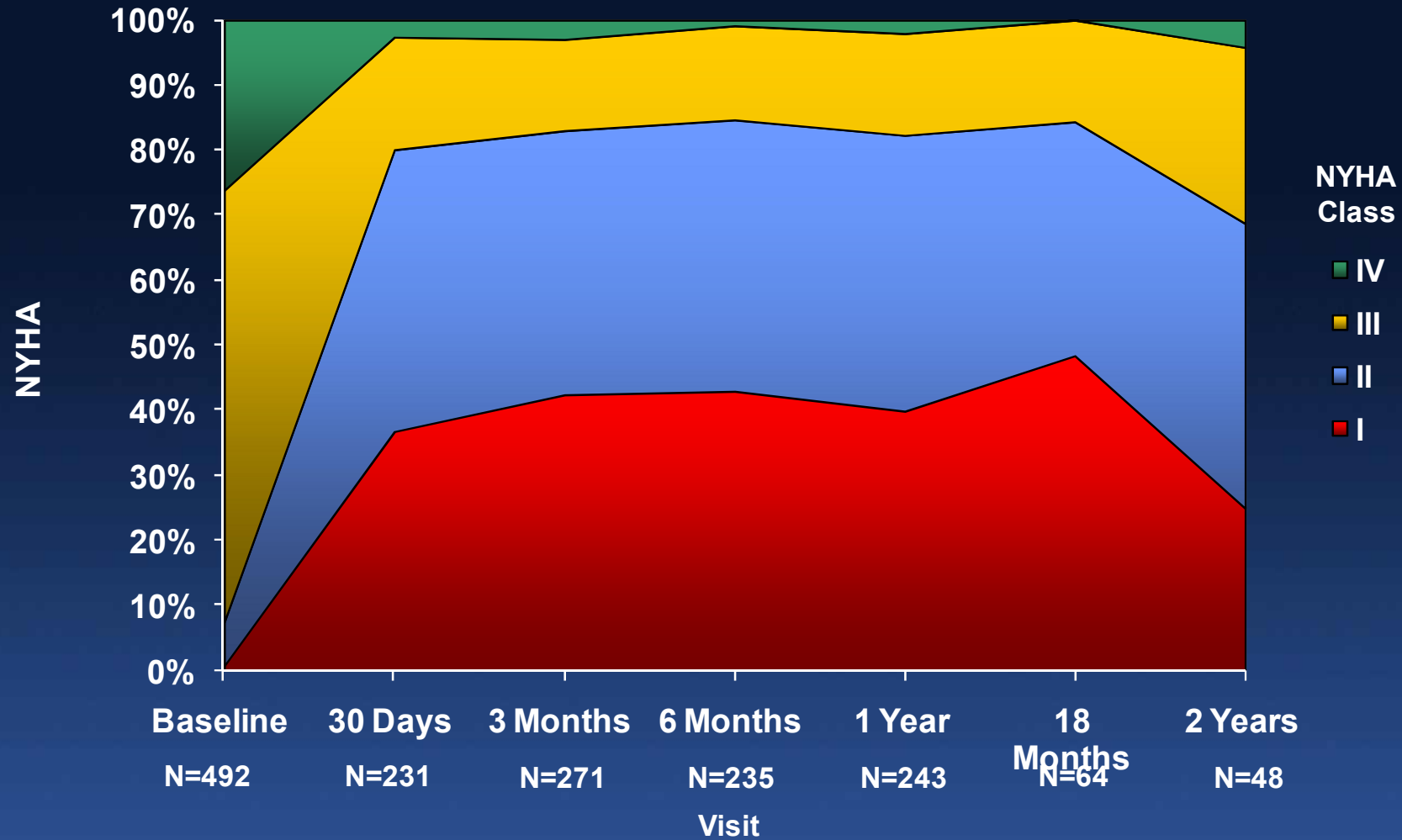
Predictor

Study (s)

- | | |
|---------------------------------|----------------------------|
| • <i>Vascular complics</i> | <i>POOLED, CA-multi</i> |
| • <i>Renal failure</i> | <i>VANCOUVER, CA-multi</i> |
| • <i>Severe MR</i> | <i>POOLED, CA-multi</i> |
| • <i>Pulmonary HBP</i> | <i>CA-multi</i> |
| • <i>Prior CABG</i> | <i>POOLED, SOURCE</i> |
| • <i>Early experience</i> | <i>VANCOUVER, PARIS</i> |
| • <i>Log EuroSCORE (>30)</i> | <i>POOLED, SOURCE</i> |

POOLED* Monitored Edwards TAVI

NYHA Class



*** REVIVE, REVIVAL, TRAVERCE
and PARTNER EU**

Vancouver TAVI Learning Experience

First Half	Second Half	Overall
10.9%	4.9%	7.9%

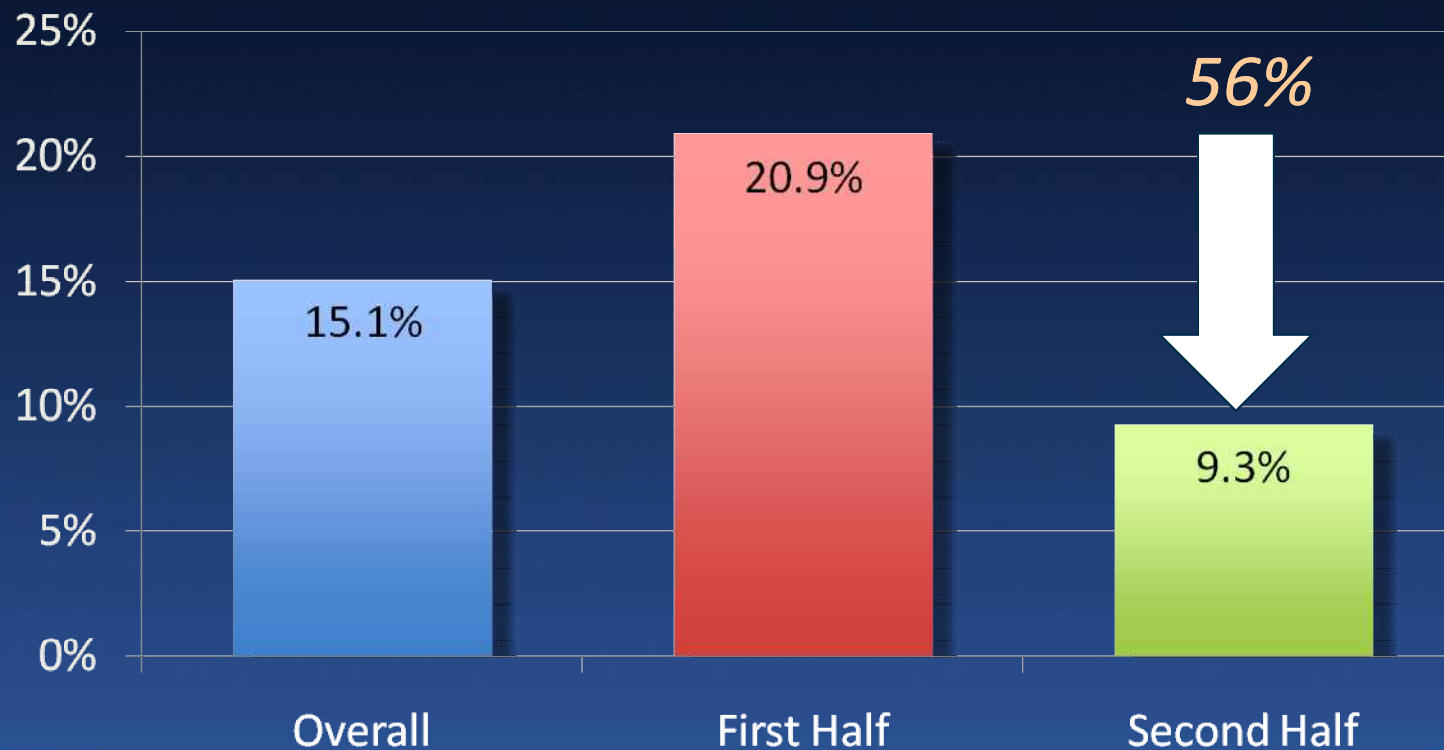
Mortality @ 30 days – Trans-arterial



Vancouver TAVI Learning Experience

First Half	Second Half	Overall
20.9%	9.3%	15.1%

Mortality @ 30 days – Trans-apical



TAVI in Evolution

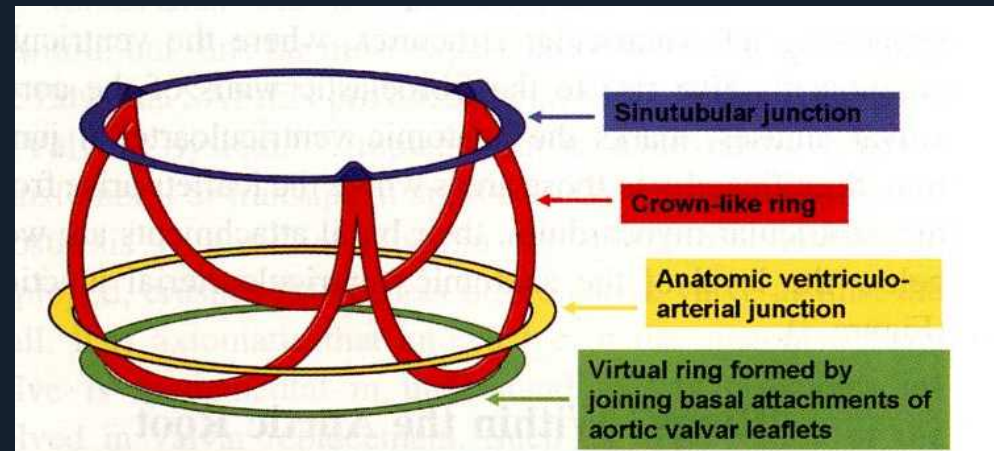
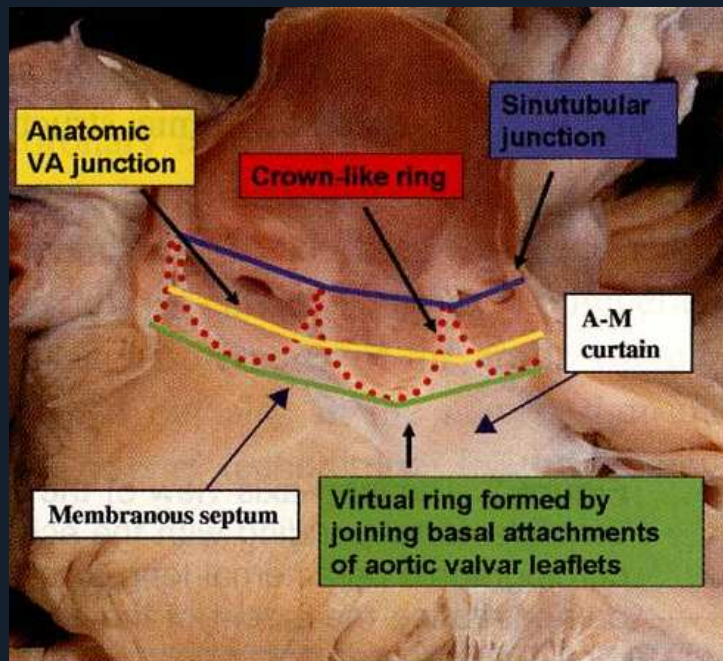
Lessons Learned...

4. *Many TAVI complications have emerged and require further analysis and clarification*

- **Paravalvular AR**
- **Conduction disturbances**
- **Vascular complications**
- **Stroke**
- **Coronary obstruction**

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*

Edwards TAVI Complications

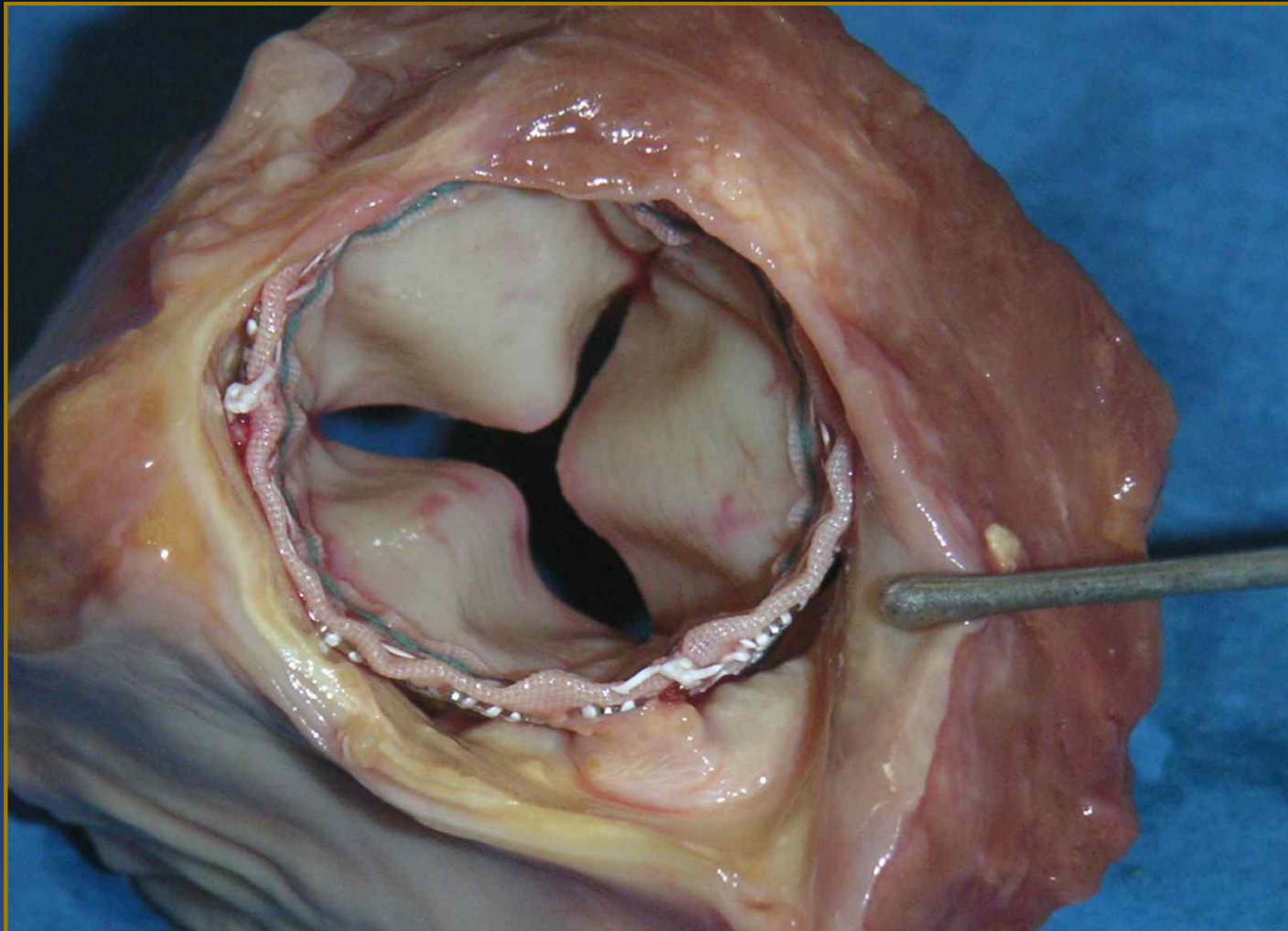
Multiple Data Sources (TA and TF)

	POOLED* (503 pts)	SOURCE (1038 pts)	VANCOUVER (250 pts)	PARIS (75 pts)	CA-Multictr (339 pts)
Vascular (maj)** (%)	18.5	10.6	10.3	11.8	13.1
AR >2+ (%)	10.9	4.7	5.0	5.3	7.7
Stroke (%)	4.0	2.5	3.0	4.0	2.3
New Pacemaker (%)	4.4	7.0	5.5	5.3	4.9
Renal Failure (%)	5.2	8.7	4.2	na	2.6
Coronary Obstr (%)	0.4	0.6	na	0	0

* REVIVE, REVIVAL, TRAVERCE, PARTNER EU

** TF Only

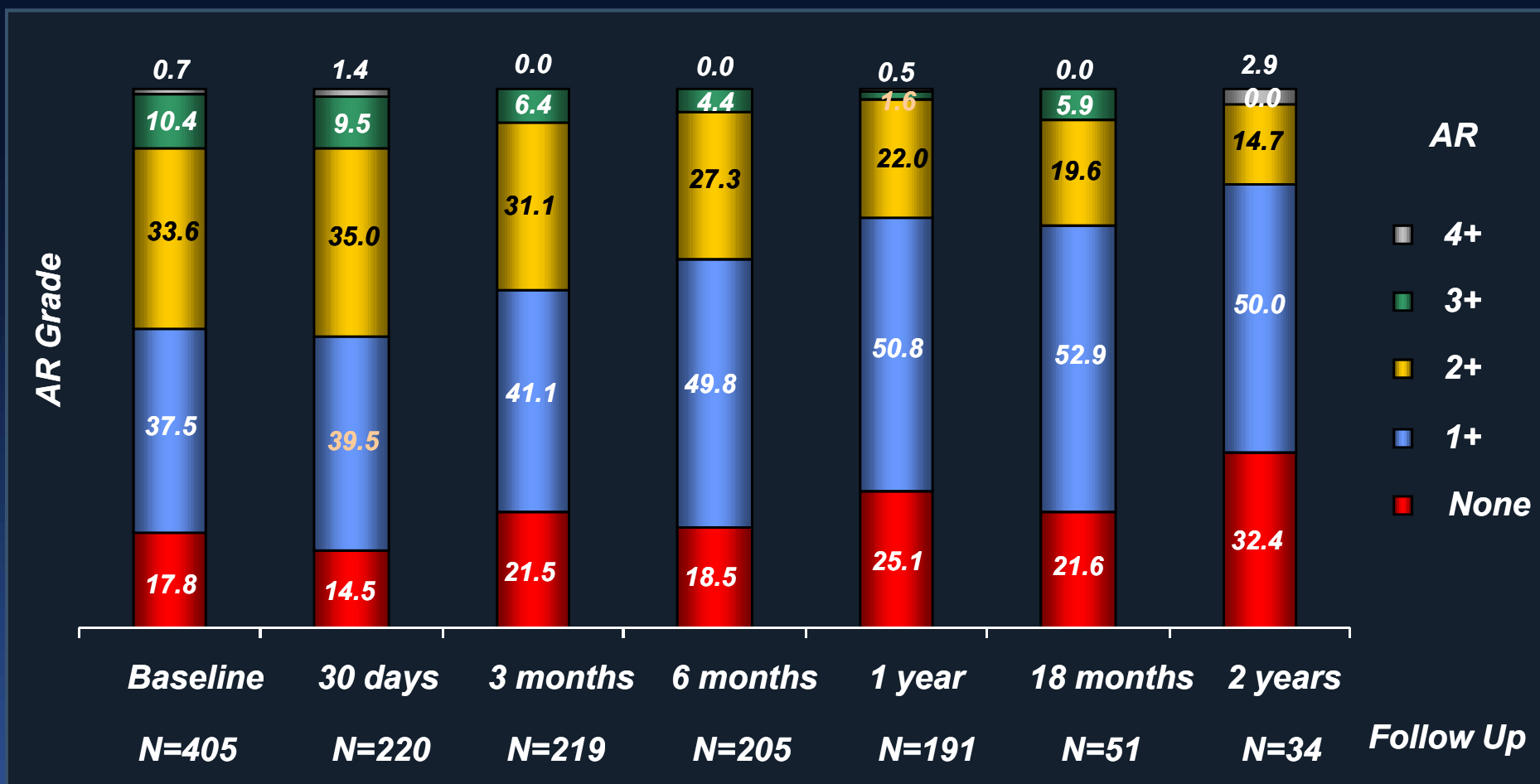
Para-valvular Regurgitation



Patient #5

POOLED* Monitored Edwards TAVI

Echo AR Results

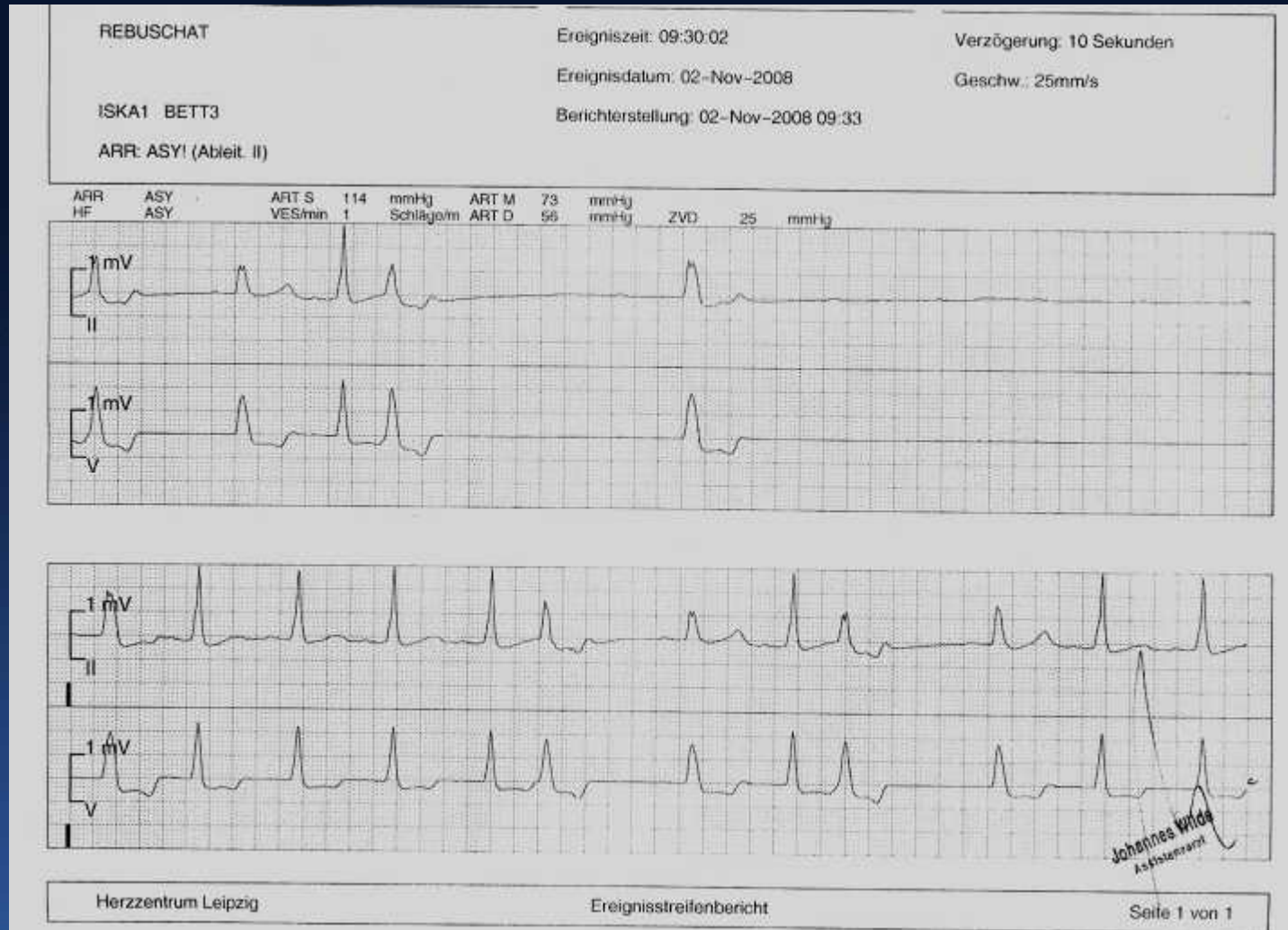


* REVIVE, REVIVAL, TRAVERCE
and PARTNER EU

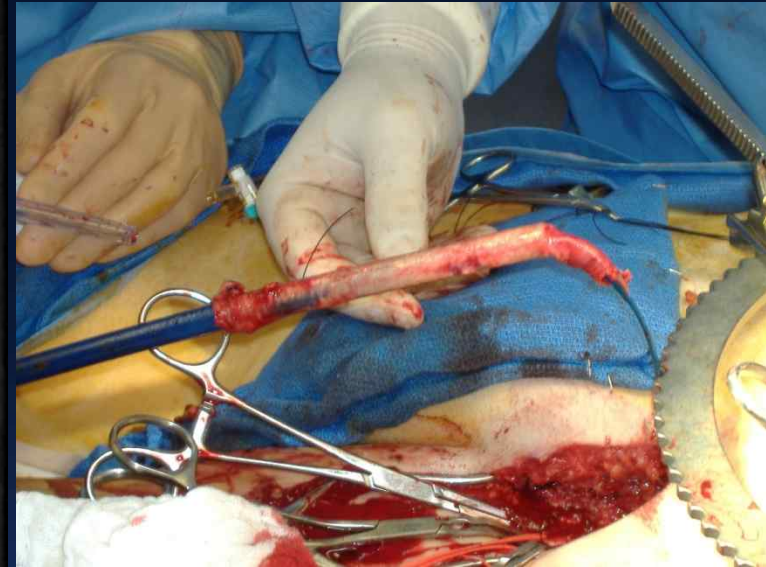
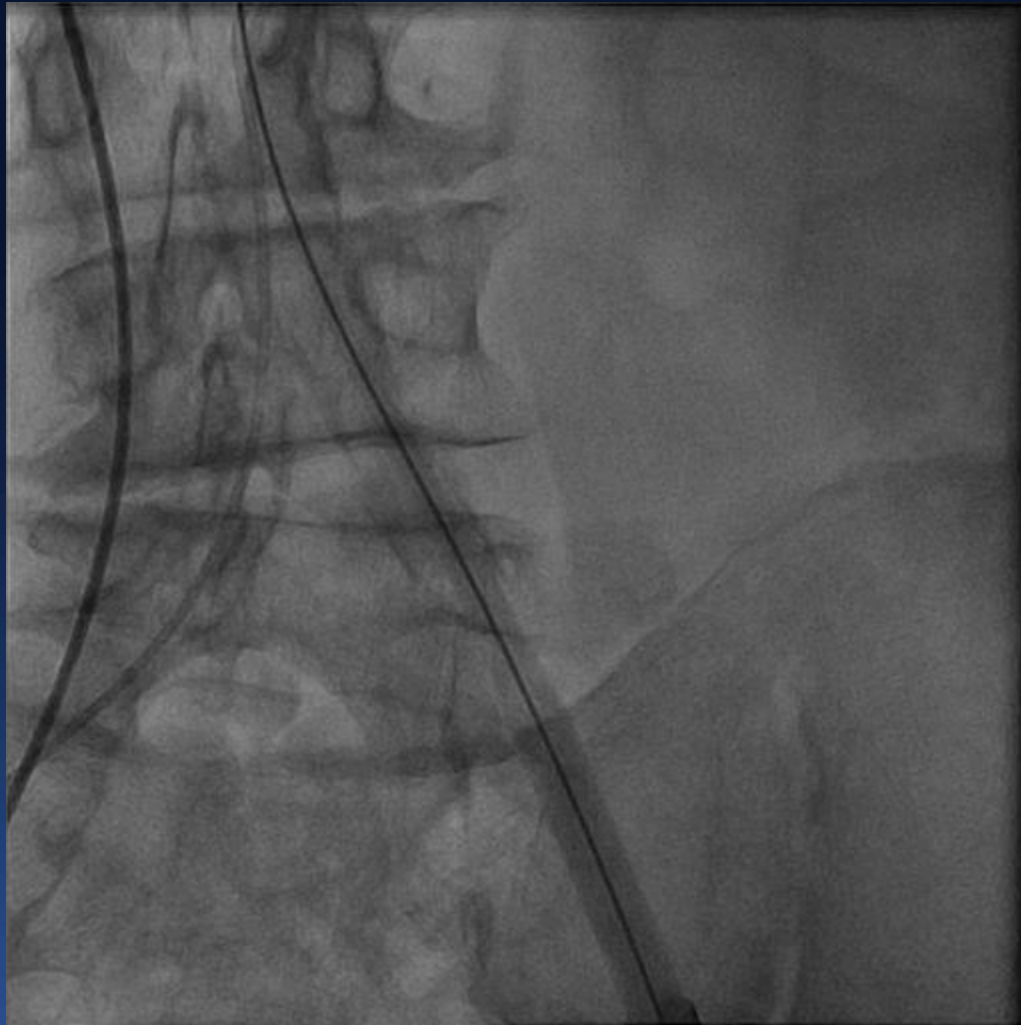
AV-Block III° Following COREVALVE Implantation



AV-Block III° Following COREVALVE Implantation



Iliac Perforation



TAVI in Evolution

Need for embolic protection...

Silent and Apparent Cerebral Ischemia After Percutaneous Transfemoral Aortic Valve Implantation: A Diffusion-Weighted Magnetic Resonance Imaging Study

Philipp Kahlert, Stephan C. Knipp, Marc Schlamann, Matthias Thielmann, Fadi Al-Rashid, Marcel Weber, Uwe Johansson, Daniel Wendt, Heinz G. Jakob, Michael Forsting, Stefan Sack, Raimund Erbel and Holger Eggebrecht

Circulation 2010;121:870-878

- **32 pts with TAVI; Diffusion-Weighted MRI at baseline, post-procedure, and @ 3 mos**
 - 22 balloon-expandable and 10 self-expanding THV devices
- **New foci of restricted perfusion in 27/32 pts (84%)**
 - Lesions usually multiple and both hemispheres (embolic)
- **No impairment of neuro-cognitive function nor clinical neurologic events assoc with MRI defects**
 - 80% of MRI defects resolved at 3 mos imaging study

Left Main Coronary Occlusion (*VF and SD after implant*)



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

TAVI in Evolution

Lessons Learned...

5. Long-term durability evaluations of TAVI bioprosthetic valves are still ongoing

- **Requires meticulous follow-up including echocardiograms (core lab assessments)**
- **Ultimate value of TAVI will mandate proof of “near surgical” long-term valve durability**

TAVI - Durability

4 year FU specimen



Edwards
~8,000 patients



Longest reported clinical follow-up (Rouen)

Mrs S..., 88 yo: > 6 years with THV



No valve dysfunction

AVA: 1.68 cm², mean gradient: 12 mmHg

TAVI in Evolution

Lessons Learned...

6. TAVI requires a major milieu adjustment to develop an optimal program

- Hybrid cath lab - ORs
- Intense clinical care continuum – screening, procedure, post-procedure care, follow-up
- Surgeons and interventionalists **MUST** work closely together!!!
- Strict training requirements

Transcatheter AVR

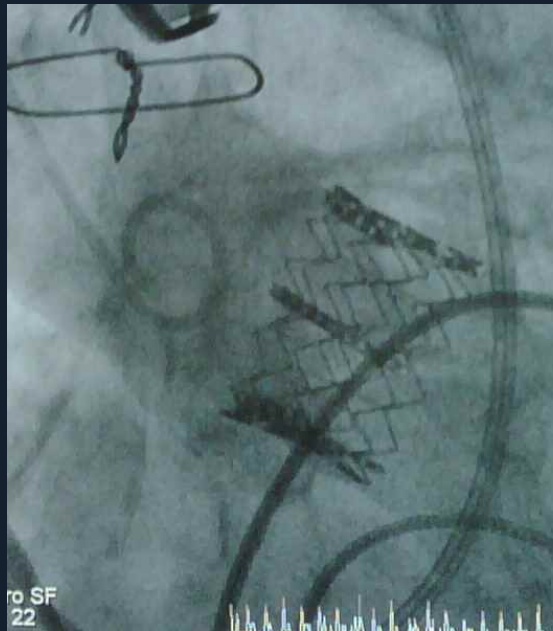
Hybrid OR-Cath Lab



A unique collaborative experience!

Transcatheter AVI

100th TAVI at Columbia...



Mat Williams
Susheel Kodali



Edwards TAVI Training Program



***Edwards THV
Training Simulator***

- ***Site preparation and staff training***
- ***Didactic and case review sessions***
- ***Complication planning***
- ***Live case observations***
- ***Patient screening oversight***
- ***Case proctoring***
- ***Critical scrutiny of clinical outcomes***

Leipzig Training Centre



Rouen Training Centre



Nyon Training Centre



TAVI in Evolution

Lessons Learned...

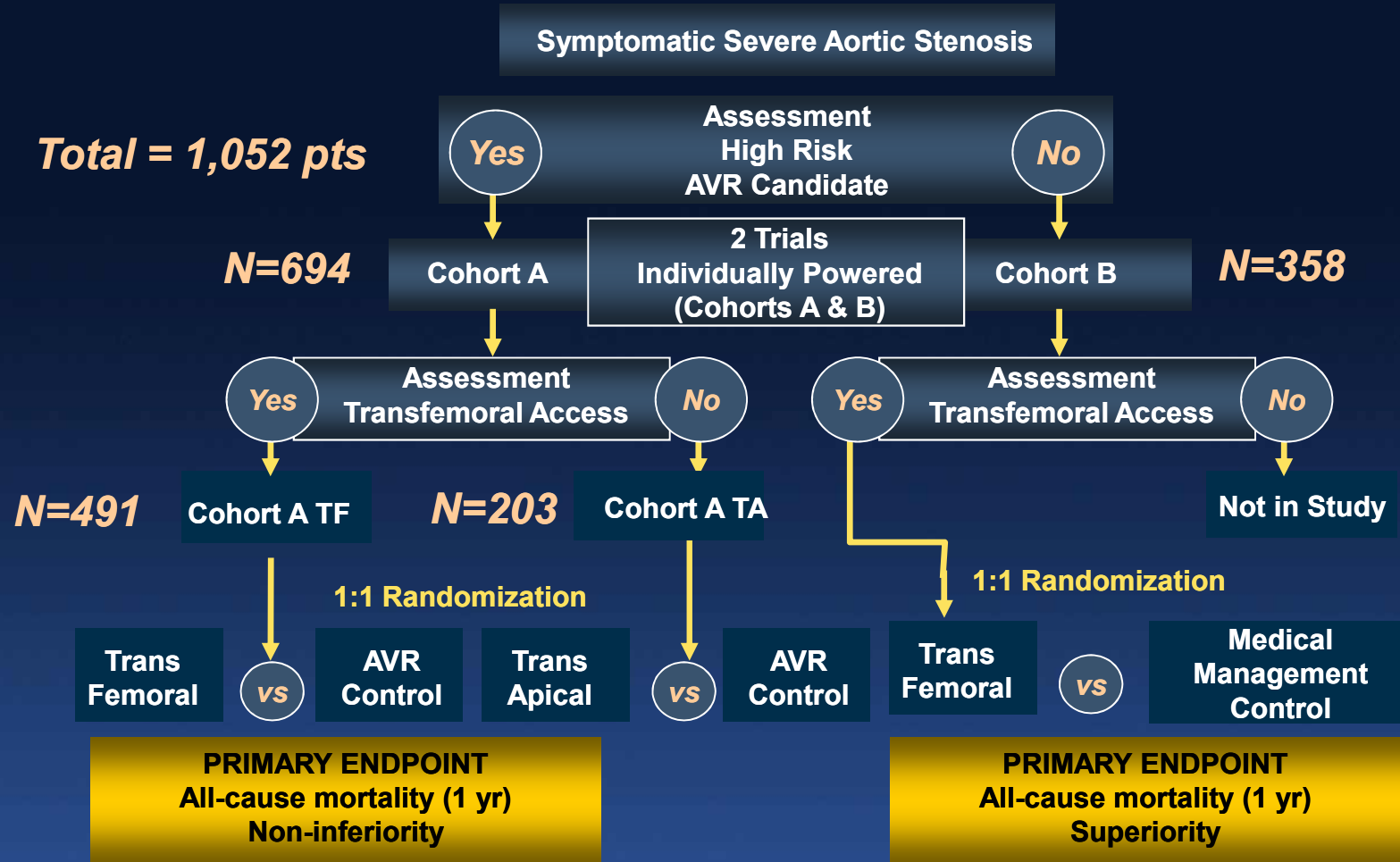
7. The PARTNER trial should provide valuable insights and (hopefully) will pave the way for future expansion of TAVI!

- **2 Randomized clinical trials (> 1,500 patients already enrolled)**
- **Rigorous clinical trial methodology**
- **Multi-disciplinary management (surgeon = interventionalist + echo)**



PARTNER Trial Design

Fully enrolled: continued access to both patient cohorts approved by FDA



PARTNER

*Baseline Characteristics**

Variable %	Cohort A-TF (test control)	Cohort A-TA (test control)	Cohort B-TF (test control)
Number of patients	450	182	430
Age (years)	83.6 ± 10.4	82.4 ± 10.8	83.1 ± 8.5
Gender (male)	58.1	57.4	48.7
Diabetes	40.2	41.7	35.4
Hyperlipidemia	79.5	79.3	74.0
Hypertension	90.0	95.4	85.3
Smoking	42.6	56.6	46.9
Prior MI	25.3	31.4	25.2

• *Preliminary snapshot*

• *Outcomes data blinded*

**subset of all randomized patients
in cohort A (TF+TA) and cohort B (incl. CA)*

PARTNER

High Risk Co-Morbidities (1)*

Variable %	Cohort A-TF (test control)	Cohort A-TA (test control)	Cohort B-TF (test control)
Number of patients	450	182	430
Periph Vasc Disease	32.7	56.2	26.8
Hx CHF	97.6	96.6	97.0
NYHA Class III/IV	94.0	91.6	93.2
Prior CABG	59.5	69.8	59.5
Prior PCI	45.7	48.4	37.2
Prior BAV	15.9	15.9	25.6
Severe COPD (O2 dep)	7.1	9.7	23.8

**subset of all randomized patients
in cohort A (TF+TA) and cohort B (incl. CA)*

PARTNER

High Risk Co-Morbidities (2)*

Variable %	Cohort A-TF (test control)	Cohort A-TA (test control)	Cohort B-TF (test control)
Number of patients	450	182	430
CNS Disease	23.0	32.0	26.9
Recent Stroke/TIA	2.5	3.6	2.4
Cirrhosis	2.0	0	2.2
Porcelain aorta	0.4	1.0	15.1
Chest radiation	0.6	1.0	7.8
Chest wall deformity	0	0	6.9
Frailty	18.9	17.6	27.9

**subset of all randomized patients
in cohort A (TF+TA) and cohort B (incl. CA)*

PARTNER

STS Score Trends

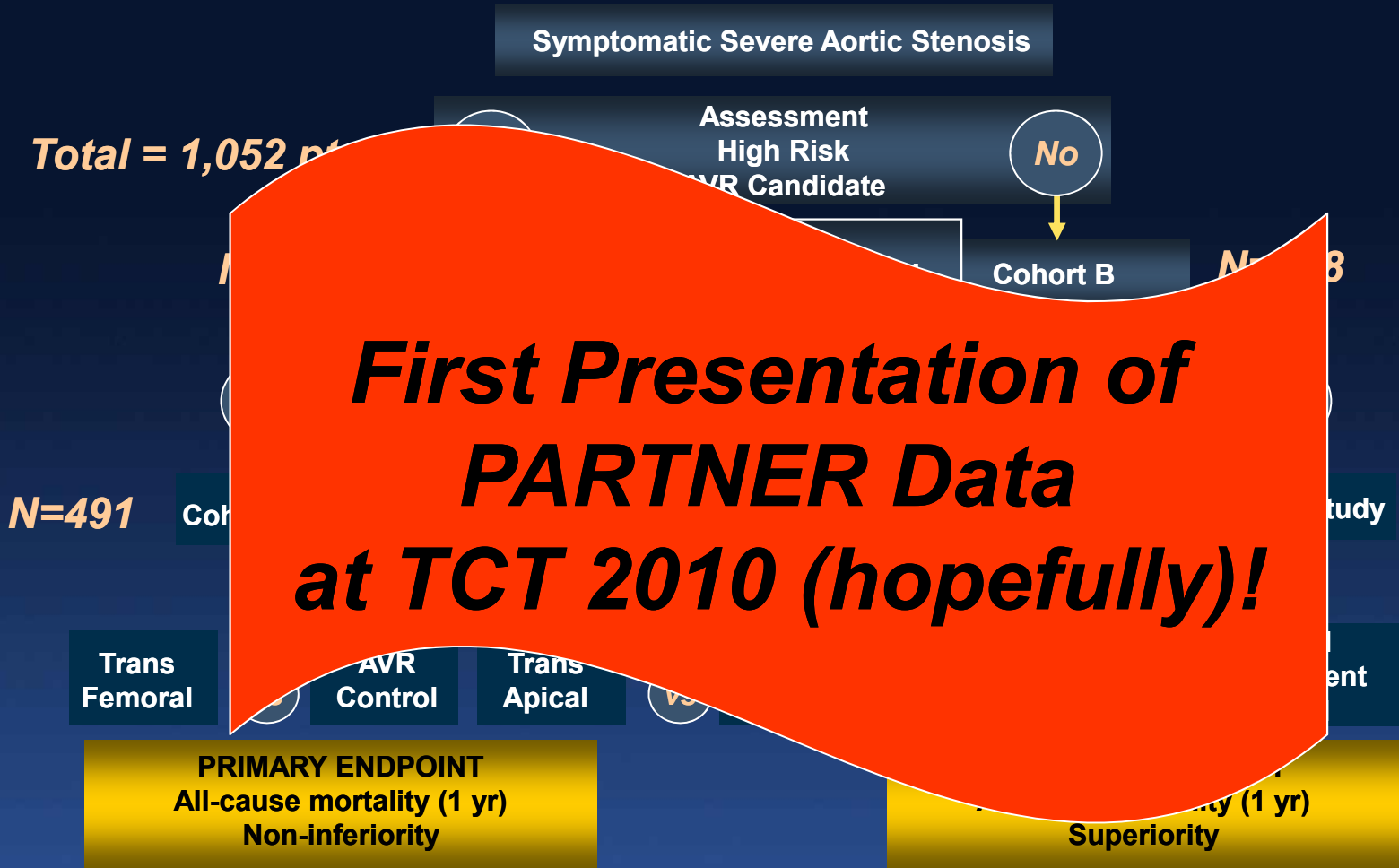
ITT Cohort	Mean	Std Dev	Lower Quartile	Median	Upper Quartile
A	11.75	3.38	10.10	11.10	13.00
*B	11.76	6.19	7.55	11.20	14.95

**Non-operable status not based solely on STS score; requires minimum of 3 cardiac surgeons assessment of non-operability*



PARTNER Trial Design

Fully enrolled: continued access to both patient cohorts approved by FDA



***First Presentation of
PARTNER Data
at TCT 2010 (hopefully)!***

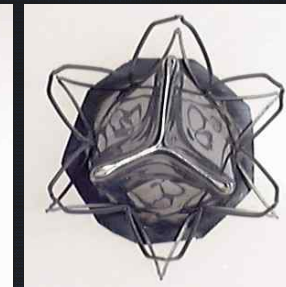
Lessons Learned...

8. *The future is exciting – TAVI procedure device enhancements (including accessories) and expanded clinical indications!*

- **New valve designs, lower profile systems, cerebral embolic protection, large hole vascular closure**
- **Highest priority – “medium” risk patients, AS + CAD, and bio-prosthesis valve failure**

New TAVI Technologies

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

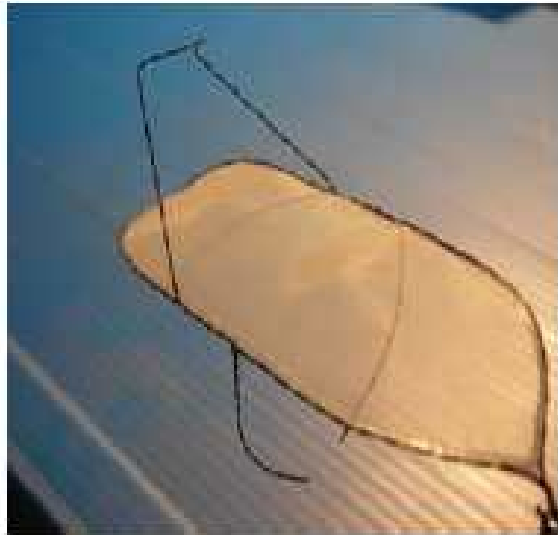


Embrella: Embolic Protection *(intra-cardiac and valve procedures)*



TAVI in Evolution

Cerebral Embolic Protection



SMT



Embrella

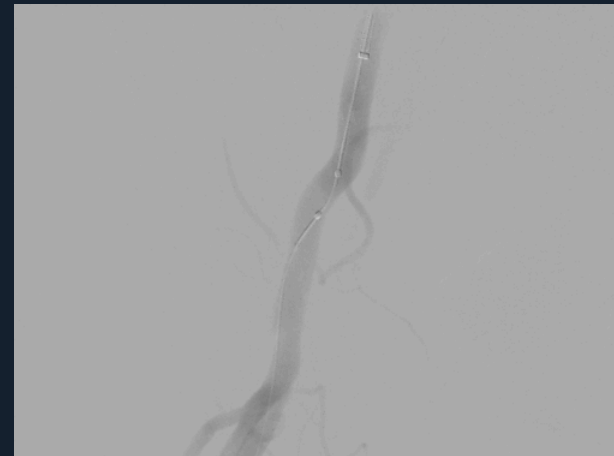
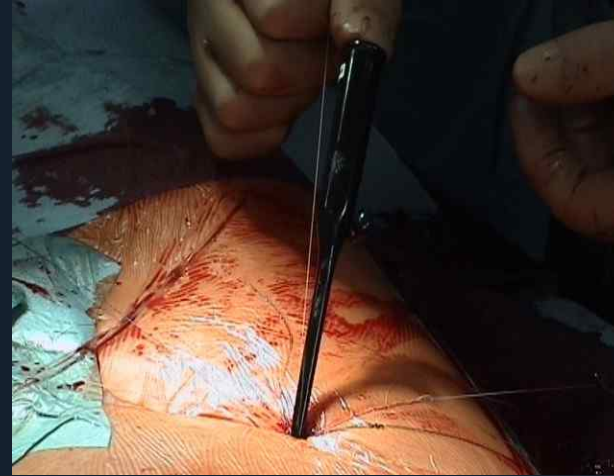


Claret

Deflectors and Filters

Percutaneous Closure

10 Fr Prostar device



TAVI in Evolution

Next Clinical Targets

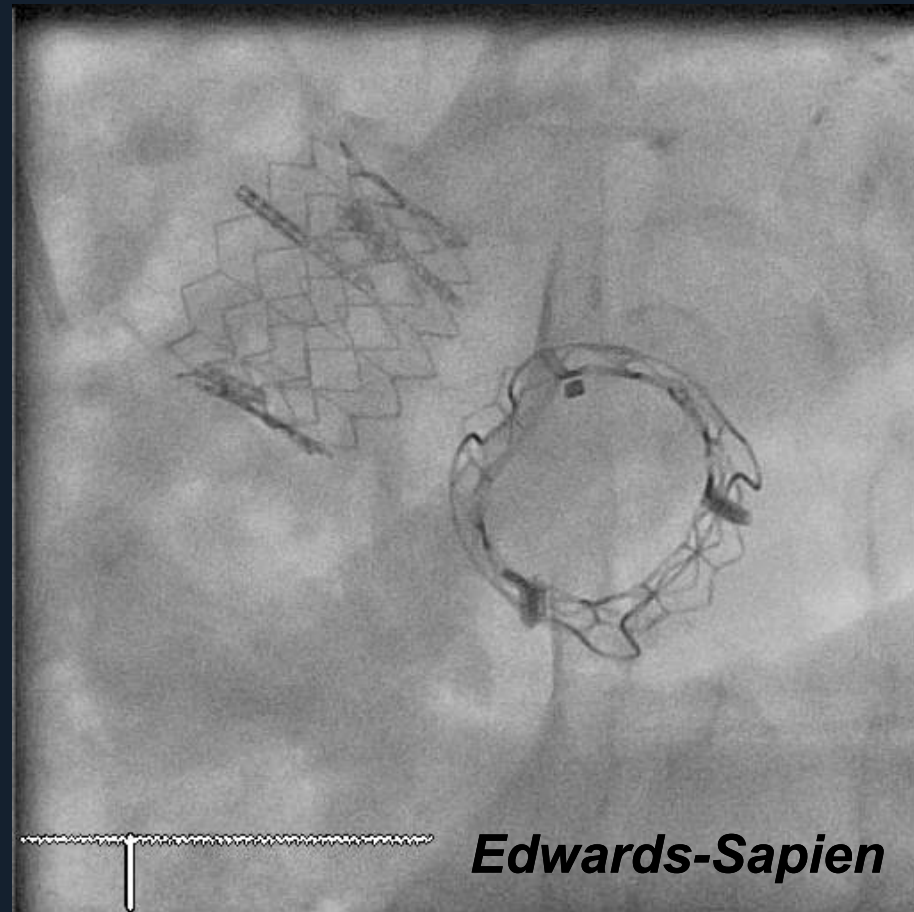
- **Valve-in-valve for bio-prosthetic aortic and mitral valve failure**
- **Lower risk AS patients**
- **Mixed AS and CAD patients**
- **Asymptomatic severe AS**
- **Low flow - low gradient AS – impedance mismatch**
- **Aortic regurgitation**

Transcatheter AVI

Endless Possibilities!

***Trans-apical
AVR***

***Trans-apical
MVR
(valve-in-valve)***



TAVI in Evolution

Lessons Learned

Final Thoughts

TAVI in Evolution

Final Thoughts...

- **Clinical “need” for TAVI in “high risk” AS patients is greater than anticipated**
- **TAVI is well beyond “proof of concept” or feasibility – already being integrated into AS clinical Rx paradigms in many parts of the world**
- **Technology and procedure have evolved rapidly and with proper training can be generalized to most clinical environments**
- **Clinical outcomes have stabilized in experienced hands (< 10% mortality at 30 days), with late mortality reflecting underlying co-morbidities**

TAVI in Evolution

Final Thoughts...

- **Undeniable early and sustained clinical benefit**
- **Valve performance has exceeded expectations, BUT need long-term durability data**
- **Multi-specialty “heart valve center” concept will be the model for optimal care**
- **Considerations for the future – further device evolution, improved clinical research methods (“VARC” initiative), judicious extension into lower risk patient categories, and careful cost-effectiveness assessments**

FOR MORE INFORMATION, PLEASE VISIT
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TCT2010

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