New York Transcatheter Valves Symposium

TAVR: How it Began, Where We Stand Today, and What Will the Future Bring?

Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City

25 mins

Disclosure Statement of Financial Interest
NY Transcatheter Valves Symposium; Dec 6, 2018

Martin B. Leon, MD

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation / Financial Relationship	Company
• Grant / Research Support	Abbott, Boston Scientific, Edwards Lifescience, Medtronic
• Consulting Fees / Honoraria	Boston Scientific, Medtronic, Gore, Meril Lifescience
• Shareholder / Equity	GDS, Mitralign, Valve Medical

Dr. Alain Cribier

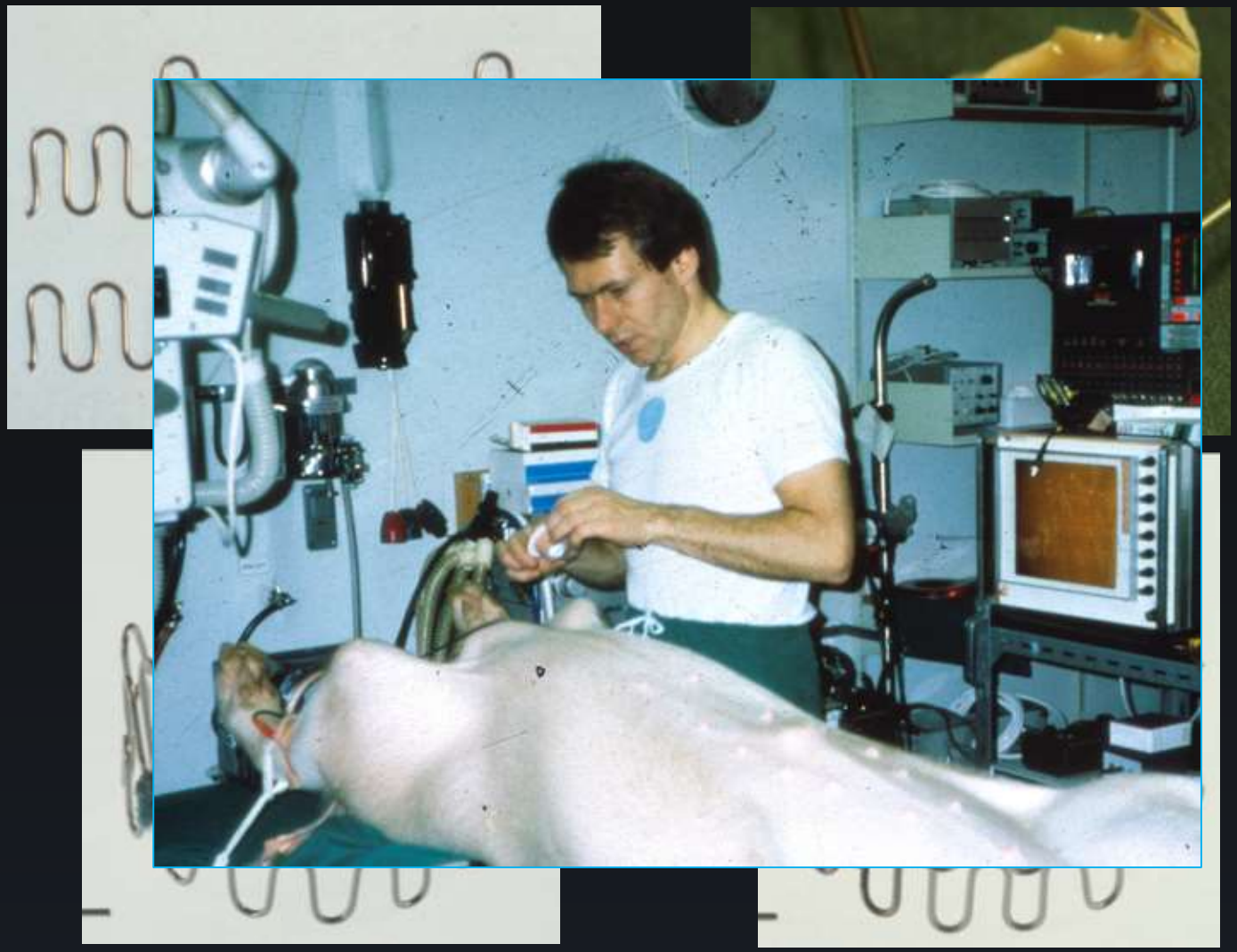
First-in-Man PIONEER

April 16, 2002

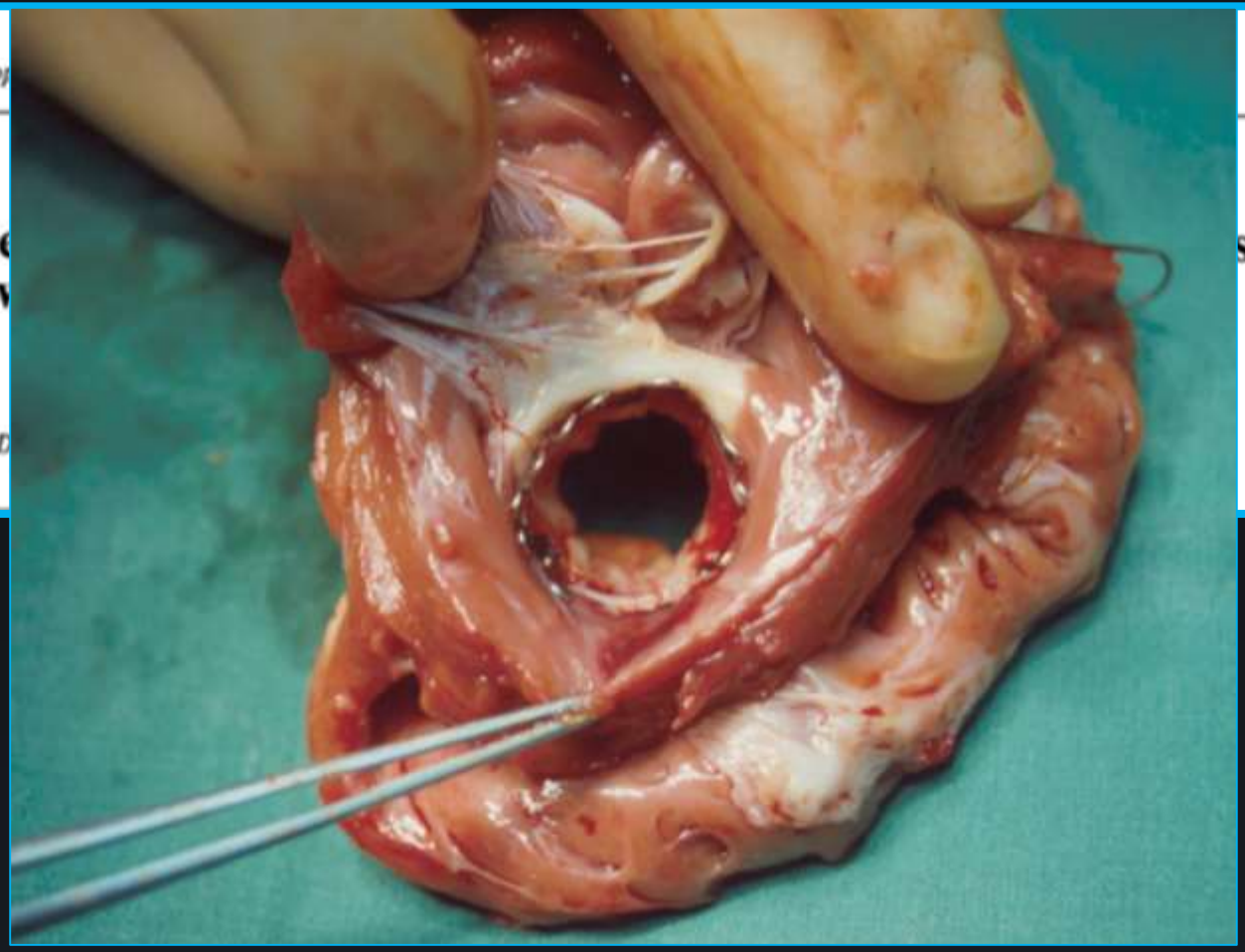
TAVR Landscape - 2018

How it began…

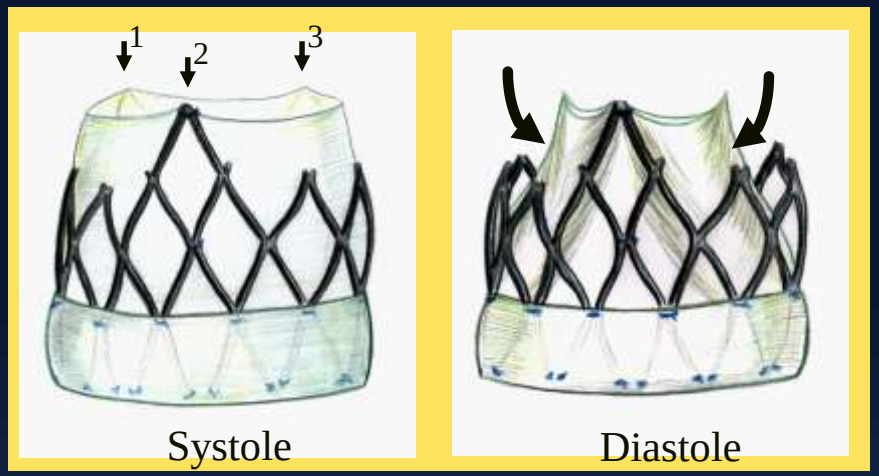
The Andersen Stent-Valve (1989)

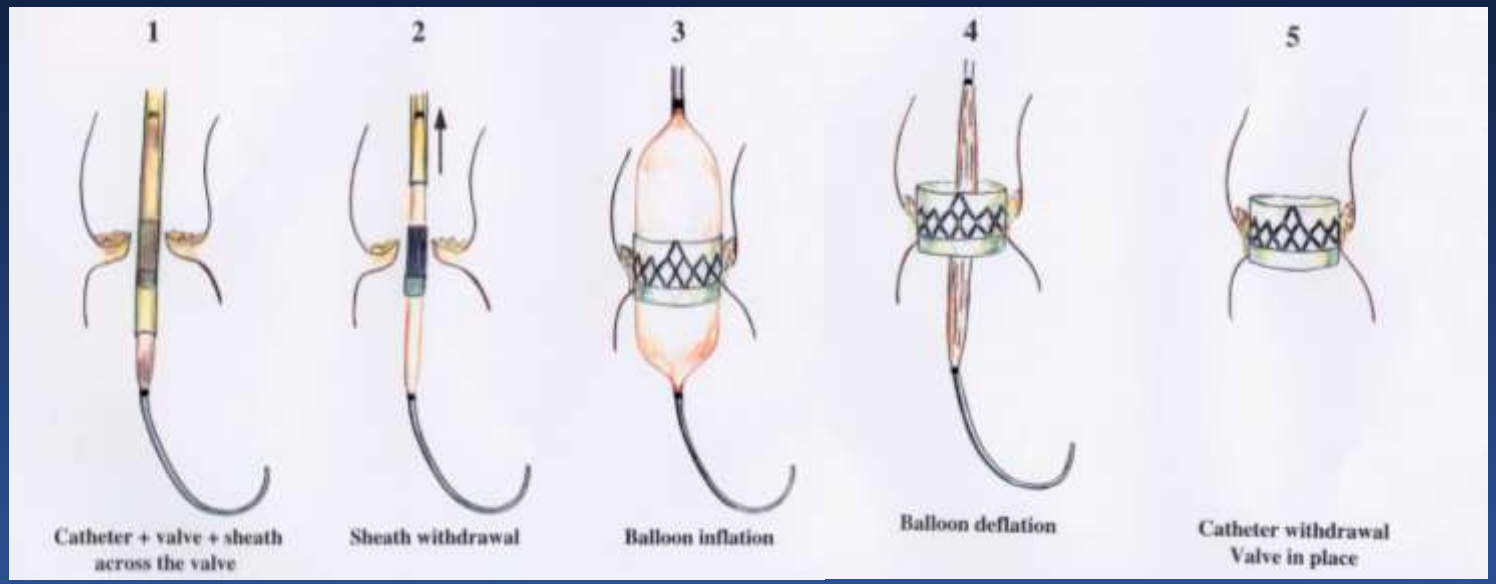


The Andersen Stent-Valve (1992)



Alain Cribier Sketches (1990)





Percutaneous Valve Technologies PVT)

(1999 - 2004)

PVT Percutaneous Valve Technologies

FOUNDERS

Martin Leon

Alain Cribier

Santon Rowe

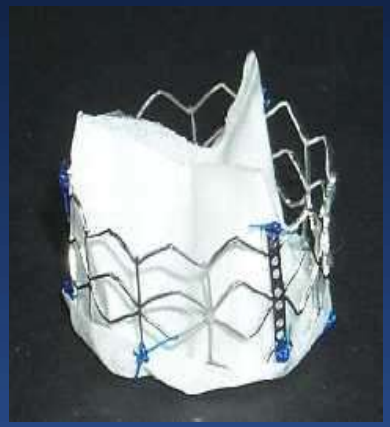
Stan Rabinovich

Partner: ARAN Research & Development Ltd.

Percutaneous Valve Technologies PVT)

Early Prototypes

- Different valve configurations
- Different leaflet materials, designs and attachment means
- Extensive hydrodynamic testing



PVT designed the testing equipment and crimping tools

PVT 2000-2002: The Sheep Era

CERA (Centre d'Experimentation et de Recherche Appliquée)
Institut Monsouris, Paris, France

PVT - Cadaver Heart Study at AFIP

TAVR Landscape - 2018

The first case in Rouen

Alain Cribier to Martin Leon, Stan Rowe, Stan Rabinovich, Assaf Bash
April 12, 2002

I have a fascinating case that I would like to discuss with you!

57 y/o

EF 10%

Transeptal BAV performed

BP 60 mmHg with vasopressors

Intra-LV thrombus

Imminent d

Valve impl… …sseptal approach !

… of the septum required

Externalization of wire

Highest risk !..

What do you think?

Martin Leon to Alain Cribier
April 12, 2002

You have my complete support to move ahead with the first PVT clinical placement in this desperately ill man.

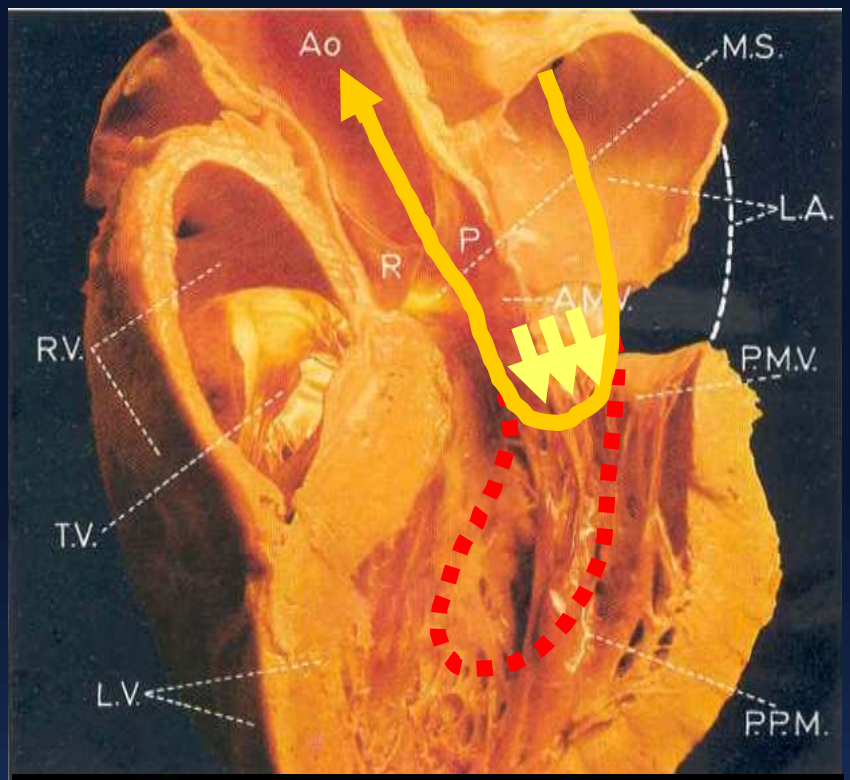
IABP?

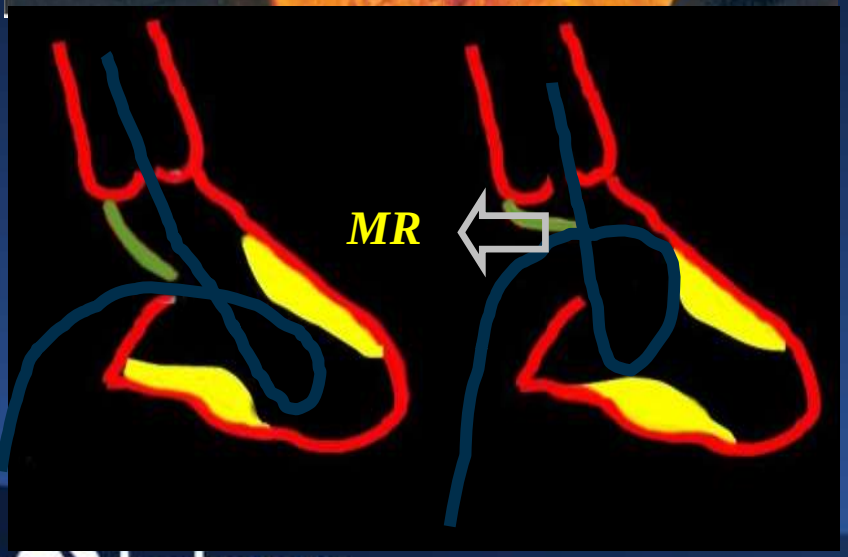
Snaring the stiff wire is a good idea

Best operator in the world!

High likehood of failure but… it just might work and save his life!

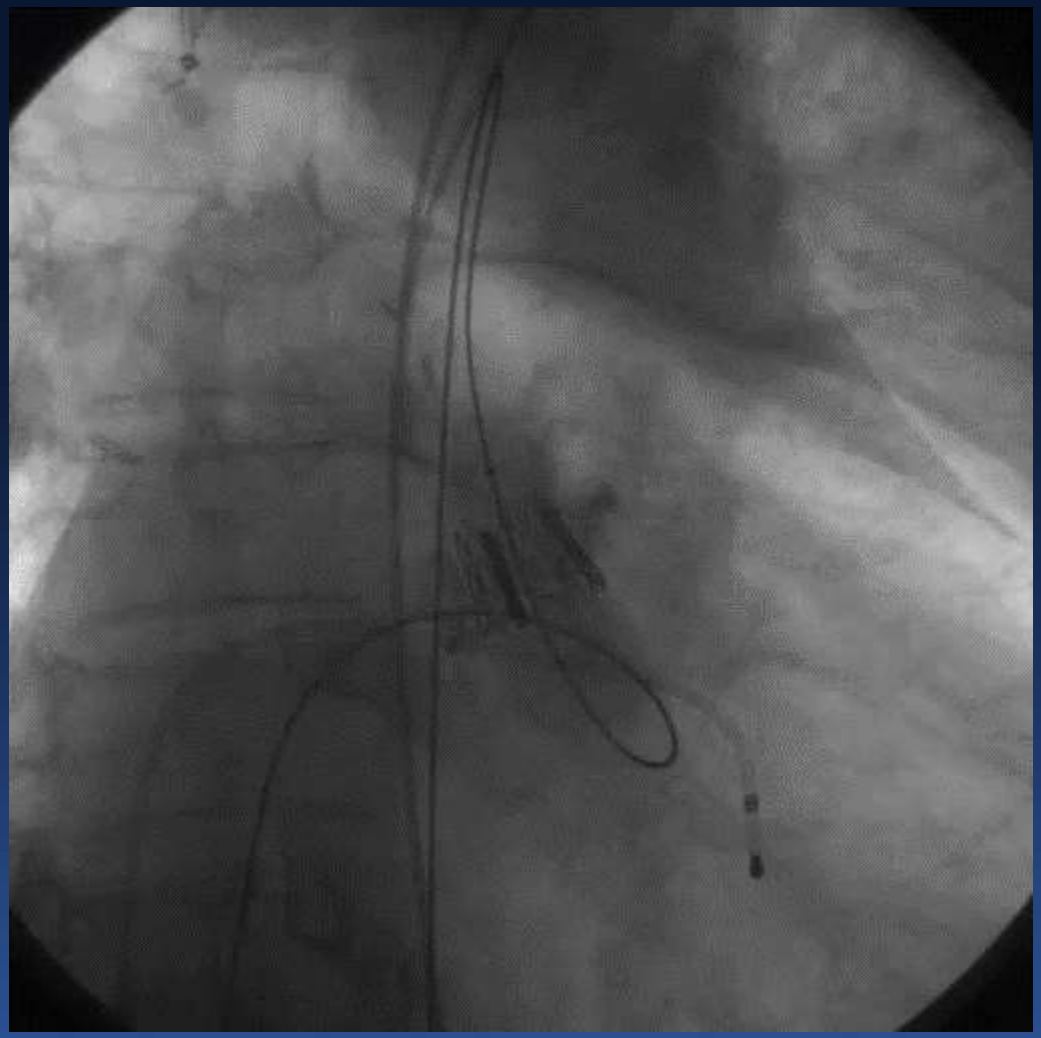
Antegrade Approach: Guidewire Position in LV



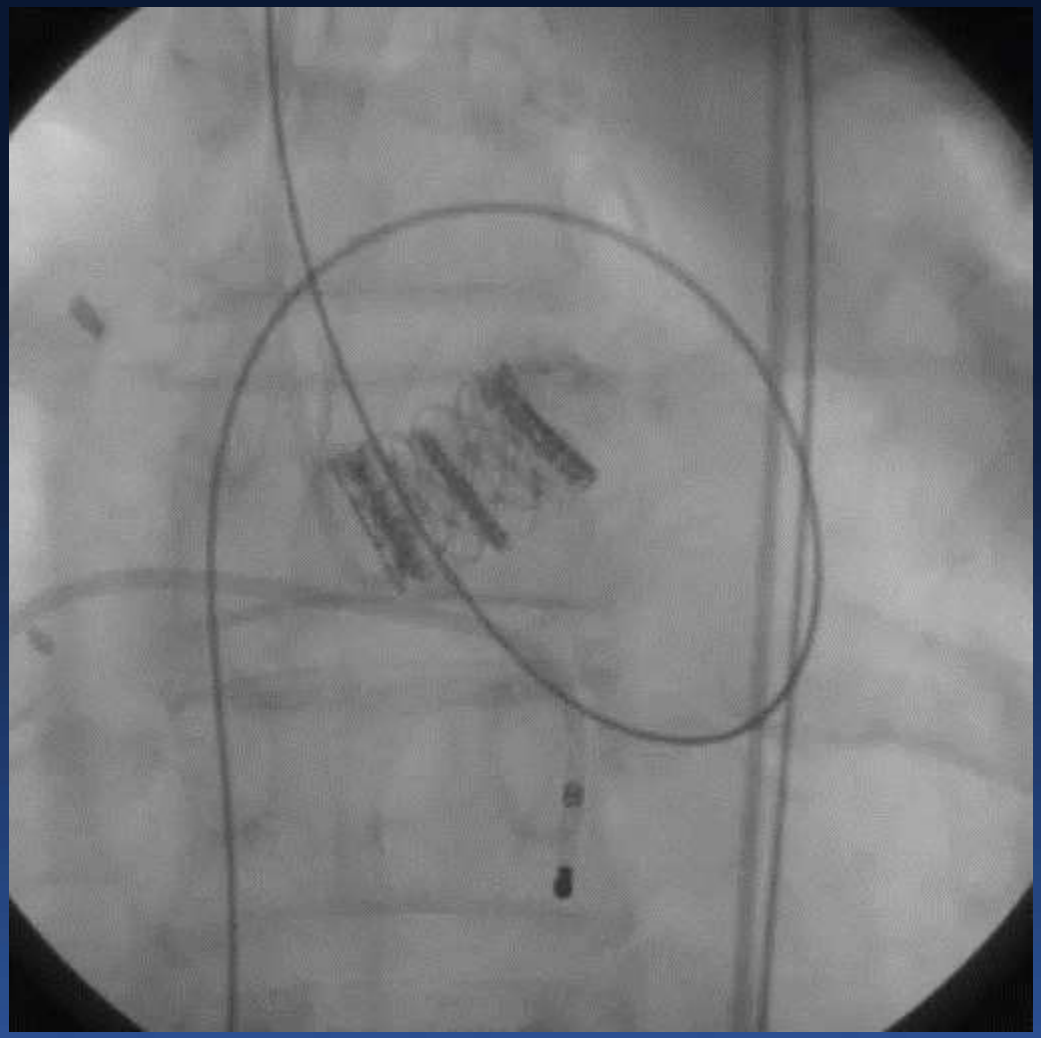



Valve Positioning

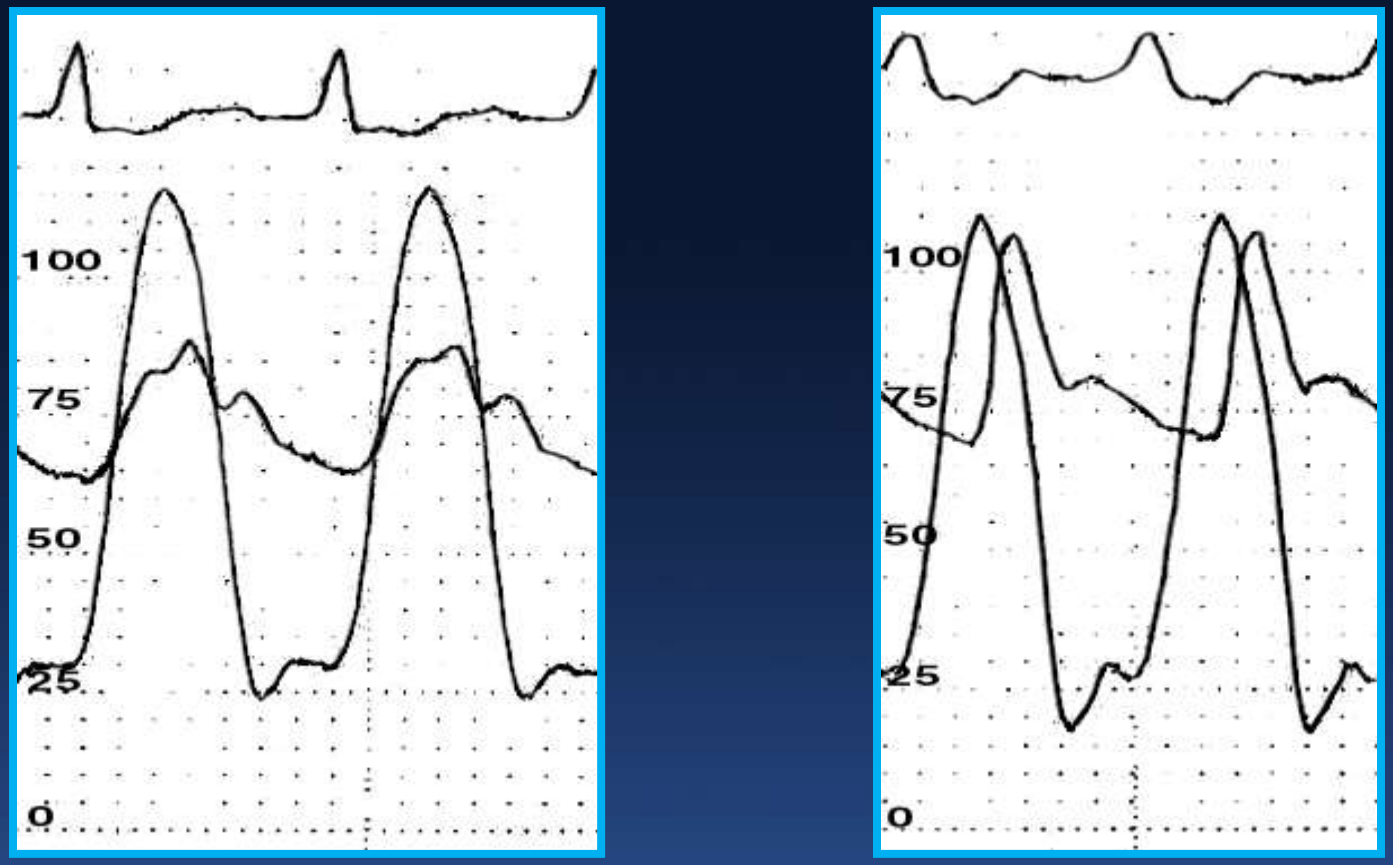
April 16, 2002; FIM-TAVI, Transseptal



April 16, 2002; FIM-TAVI, Transseptal



April 16, 2002; FIM-TAVI, Transseptal



Improvement in trans-vavular gradient!

April 16, 2002; FIM-TAVI, Transseptal

It works !!!

Dr. Alain Cribier

First-in-Man PIONEER

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
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

TAVR - The Early Skeptics

- Strokes
- Aortic rupture
- Coronary occlusion
- Mitral valve injury
- Valve instability – embolization
- Para-valvular regurgitation
- Vascular complications
- Valve durability
- Technical challenges insurmountable

This is a crazy project that will fail!

TAVR Landscape - 2018

Key Messages

- **After the landmark FIM case by Alain Cribier, the next several years were spent replicating and refining the TAVR procedure in extreme-risk patients (I-REVIVE/RECAST and REVIVAL feasibility registries in EU and US).**

Transfemoral Retrograde TAVR

Collaboration across the seas….

Drs. John Webb and Alain Cribier

Trans-apical TAVR

A deal with the devil?

Drs. Michael Mack and Fred Mohr

TAVR Landscape - 2018

Where we stand today…

TAVR Landscape - 2018

Key Messages

- After the landmark FIM case by Alain Cribier, the next several years were spent replicating and refining the TAVR procedure in extreme-risk patients (I-REVIVE/RECAST and REVIVAL feasibility registries in EU and US).
- Despite the early success of TAVR in extreme risk patients, no one could have predicted the evolution of TAVR into a mainstream therapy with a profound impact on CV medicine!

TAVR Landscape - 2018

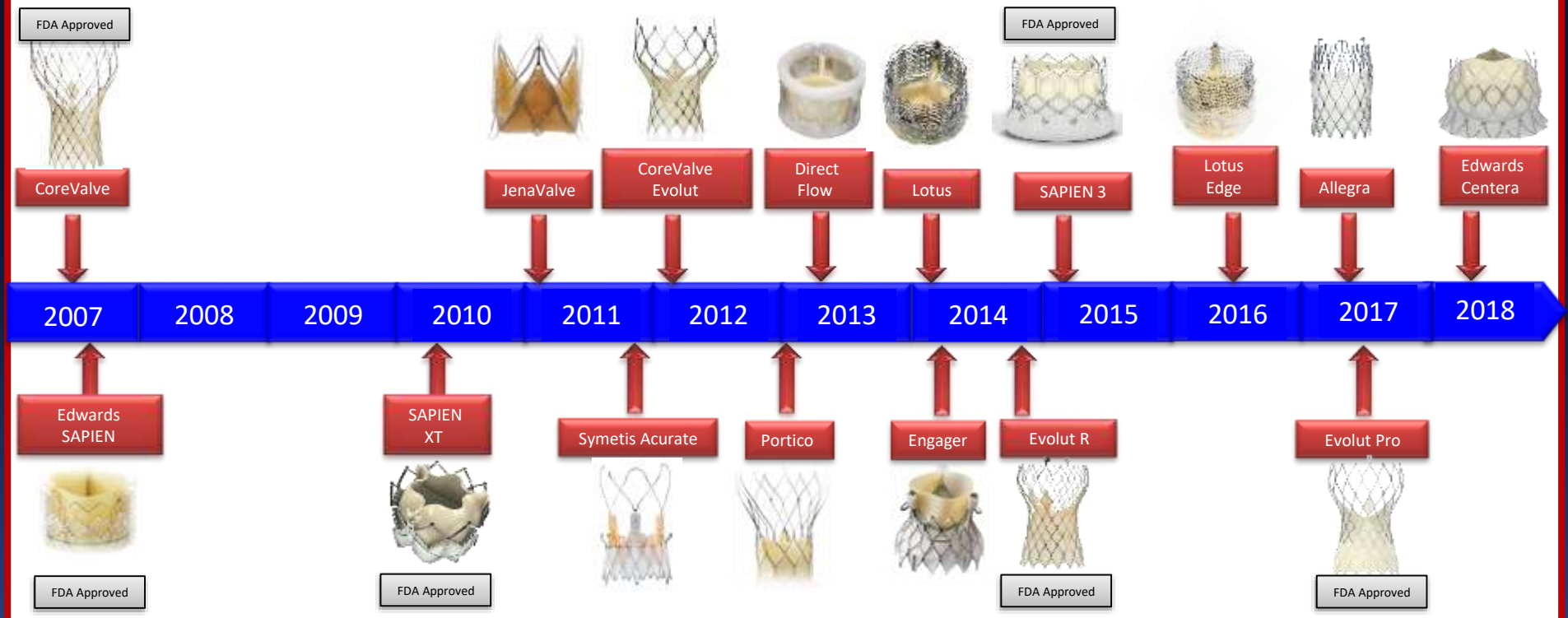
Key Messages

Reasons for TAVR Success…

1. Rapid technology evolution
2. Procedural refinements and simplification
3. Avalanche of clinical evidence
4. Heart valve team acceptance
5. Explosive growth worldwide

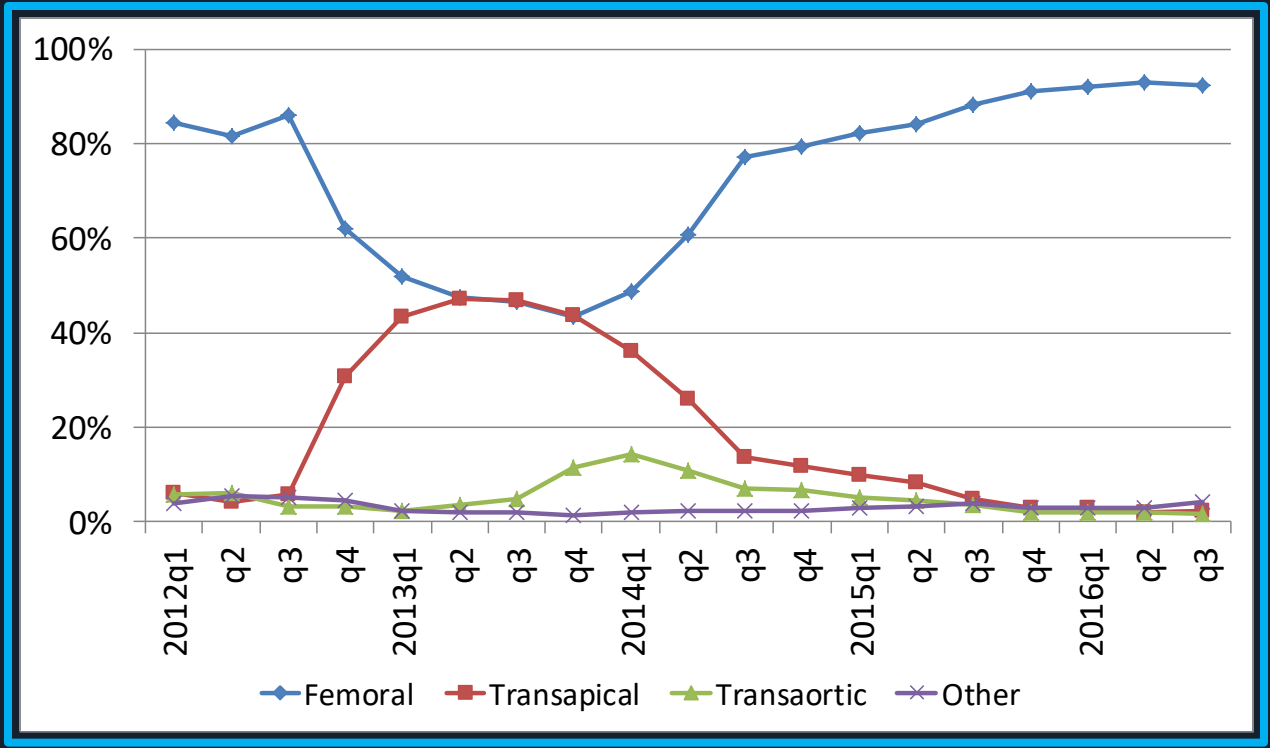
TAVR Technology Evolution

Conformité Européene (CE) Mark TAVR Systems



Non-Approved TAVR Systems

TAVR Access Evolution



TF TAVR clearly reigns supreme!

Source: STS/ACC TVT Registry Database.
79,714 records as of Jan 18, 2017

TAVR Procedure Simplification

The Minimalist Strategy

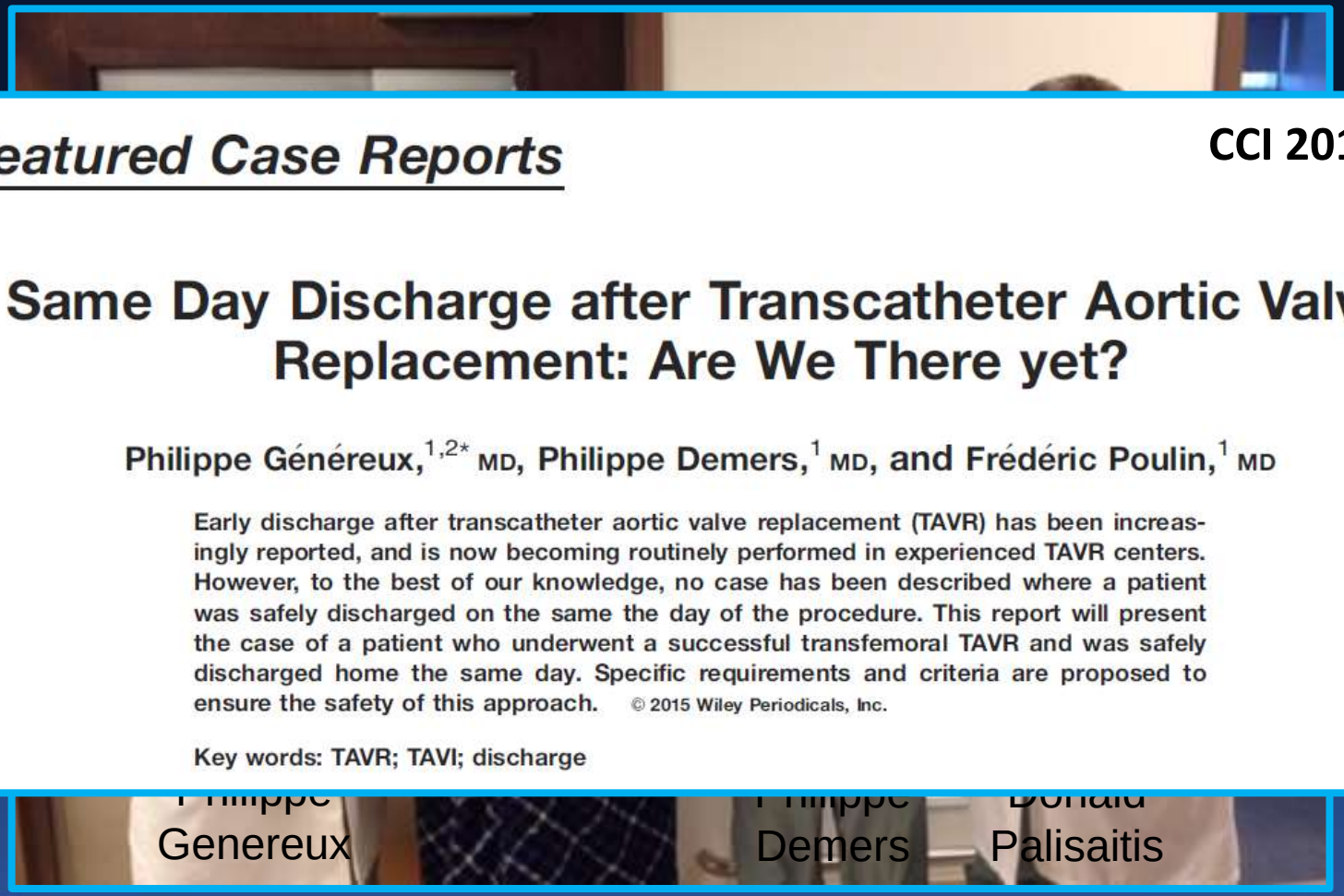
- No general anesthesia; use "conscious sedation"
- [illegible]
- [illegible]
- [illegible]
- [illegible]
- [illegible] ICUs… monitor in recovery area
- Rapid ambulation and early discharge plans (1-2 dys)

Almost all TAVR cases worldwide are now candidates for some version of "minimalist" procedural strategy!

Median LOS after TAVR is 1-2 days at Columbia-NYP Hospital!

“Outpatient” Same-Day TAVR

Sacre-Coeur Hospital; Montreal, CN



CCI 2016

Featured Case Reports

Same Day Discharge after Transcatheter Aortic Valve Replacement: Are We There yet?

Philippe Généreux,[1,2*] MD, Philippe Demers,[1] MD, and Frédéric Poulin,[1] MD

Early discharge after transcatheter aortic valve replacement (TAVR) has been increasingly reported, and is now becoming routinely performed in experienced TAVR centers. However, to the best of our knowledge, no case has been described where a patient was safely discharged on the same the day of the procedure. This report will present the case of a patient who underwent a successful transfemoral TAVR and was safely discharged home the same day. Specific requirements and criteria are proposed to ensure the safety of this approach.

Key words: TAVR; TAVI; discharge

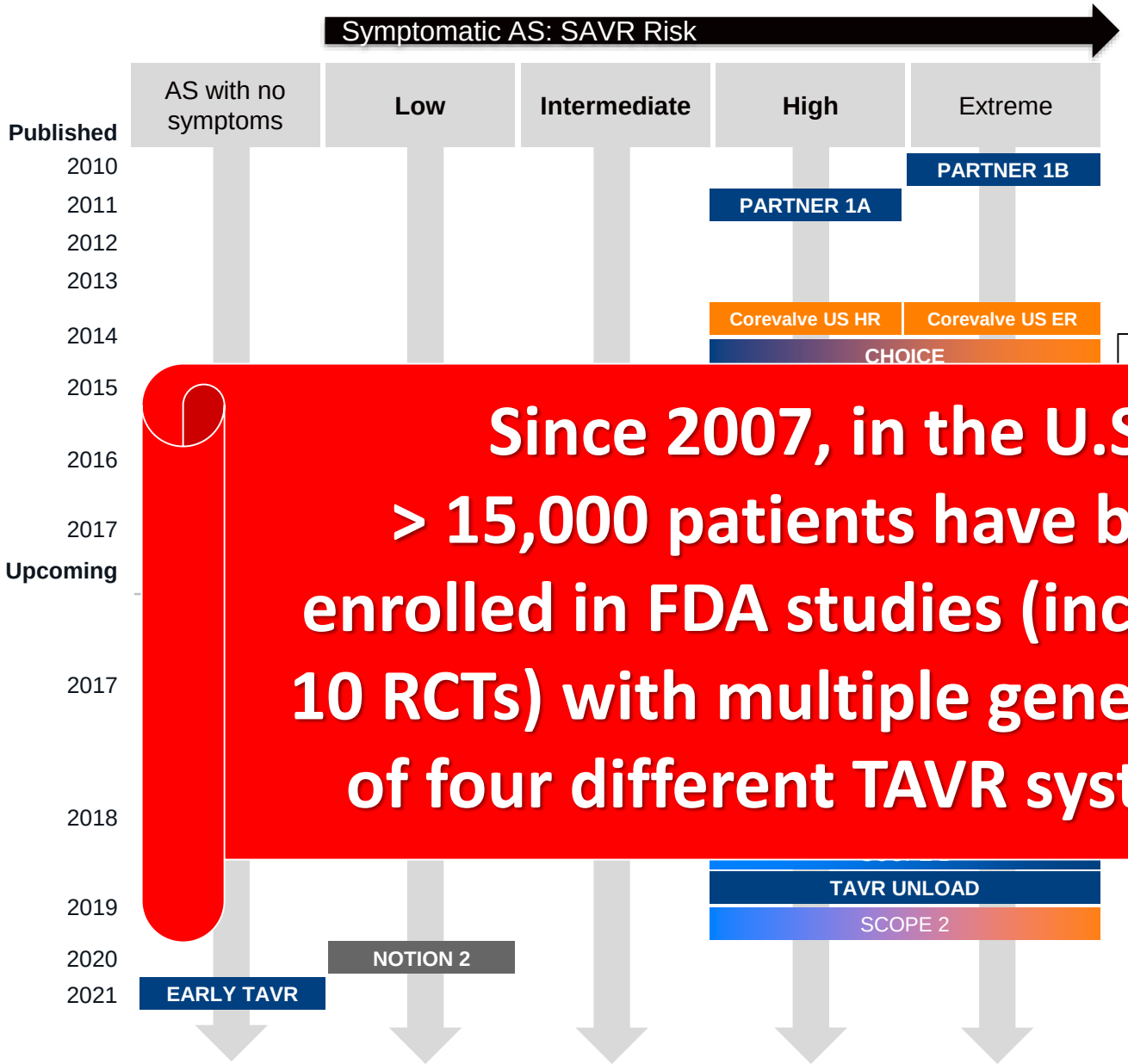
Philippe Genereux

Philippe Demers

Donald Palisaitis

Genereux P et al. CCI 2016;87:980-2

Pipeline of TAVR Trials across the spectrum of aortic stenosis

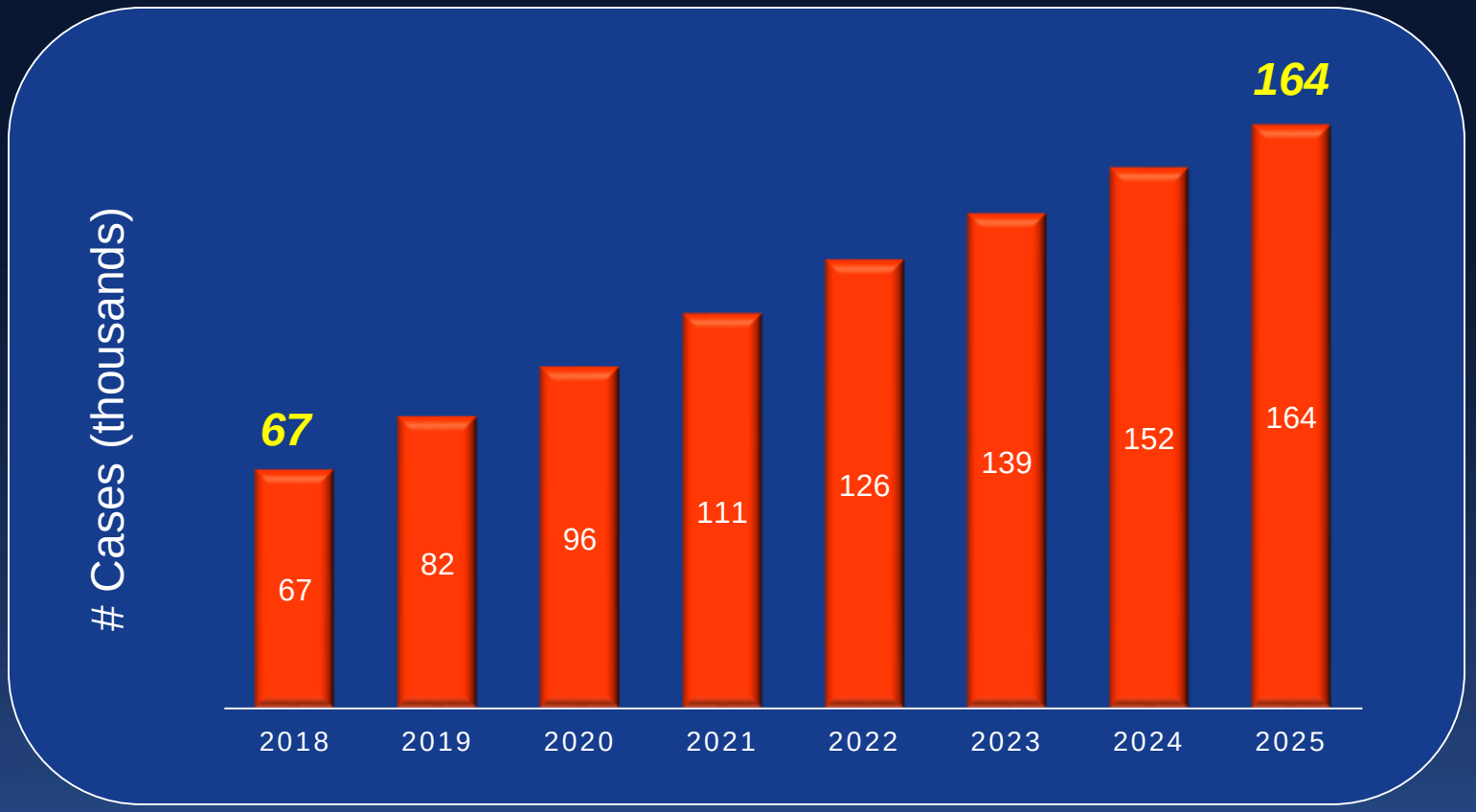


Since 2007, in the U.S., > 15,000 patients have been enrolled in FDA studies (including 10 RCTs) with multiple generations of four different TAVR systems!

24 TAVR RCTs

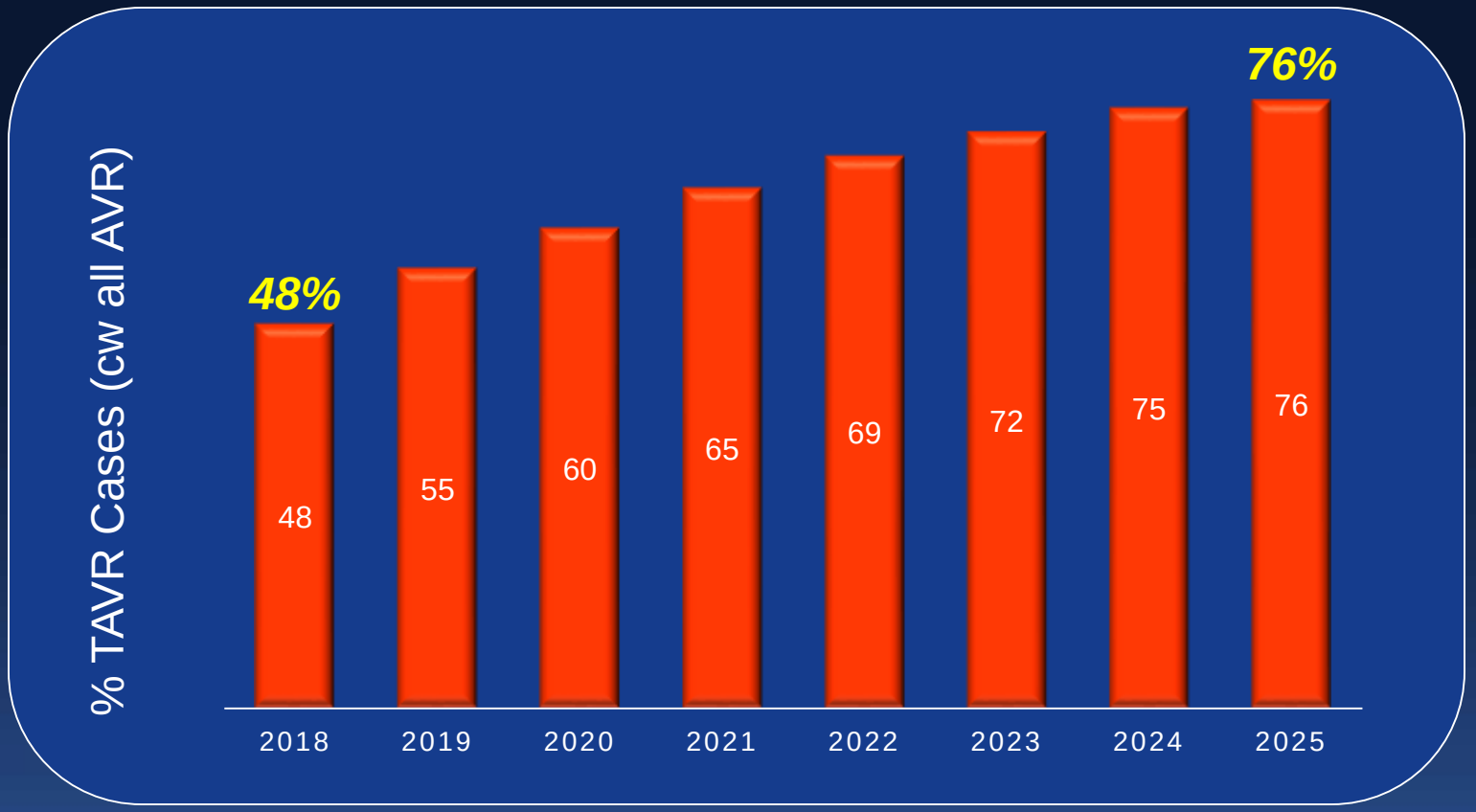
The Heart Team 3.0

Estimated US TAVR Growth



2018 - 2025 the US TAVR Market will Increase 2.5X!

Estimated US TAVR Growth



In the US, by 2025, >75% of all AVR will be TAVR!

TAVR Landscape - 2018

Key Messages

- **The VARC initiative set the stage for PARTNER, which arguably became the most successful sequence of clinical trials EVER!**

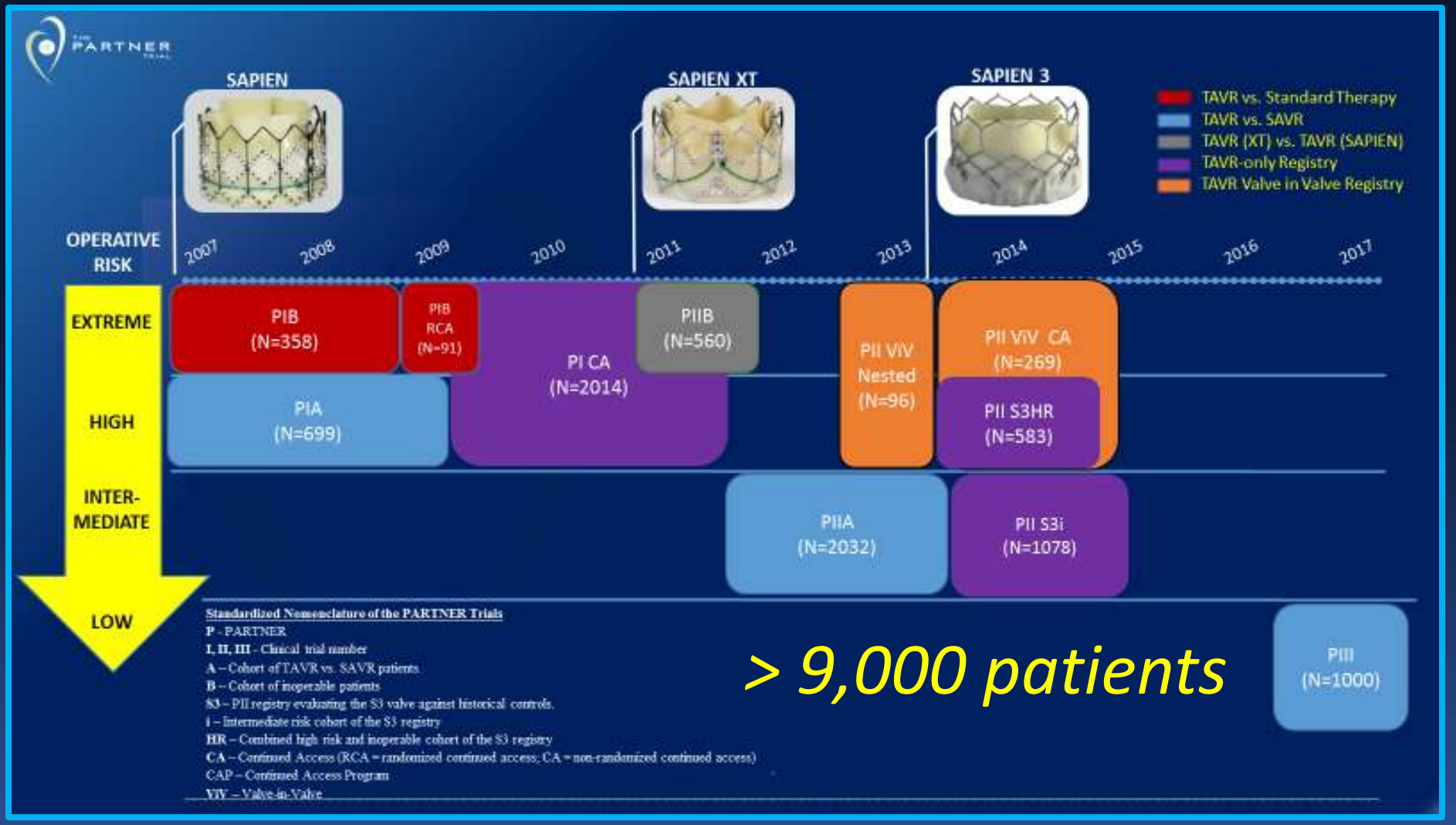
TAVR and SAVR Endpoint Guidelines

PARTNER Heart Valve Team

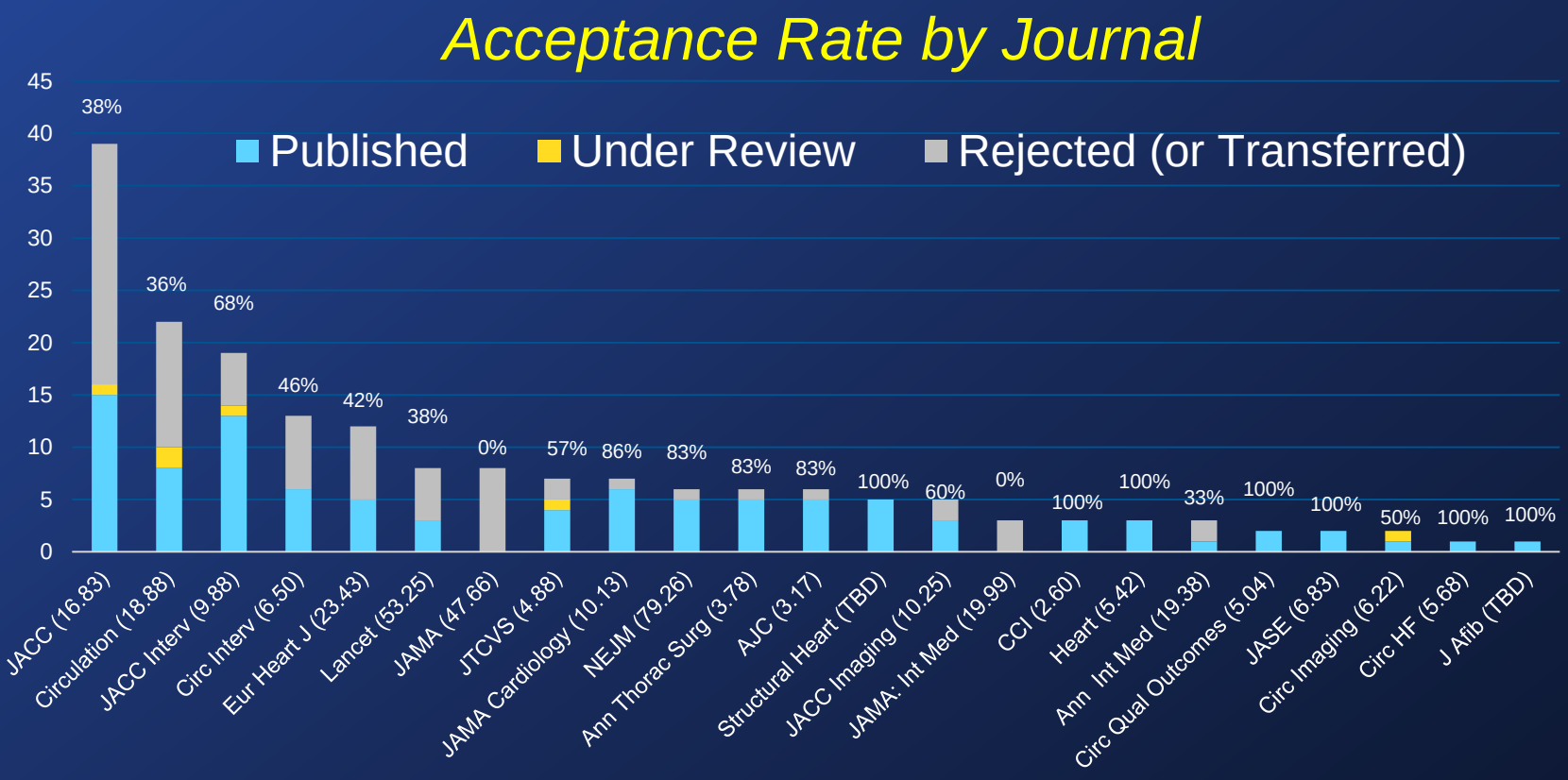
(Executive Committee)

Jeff Moses Marty Leon John Webb Michael Mack

The PARTNER Trials



PARTNER Publications Office (PPO) as of 11/26/18 (Maria Alu)



Total Manuscripts Published: 100 (23 different journals)
Total Abstracts Presented: 120 (12 distinct scientific symposia)

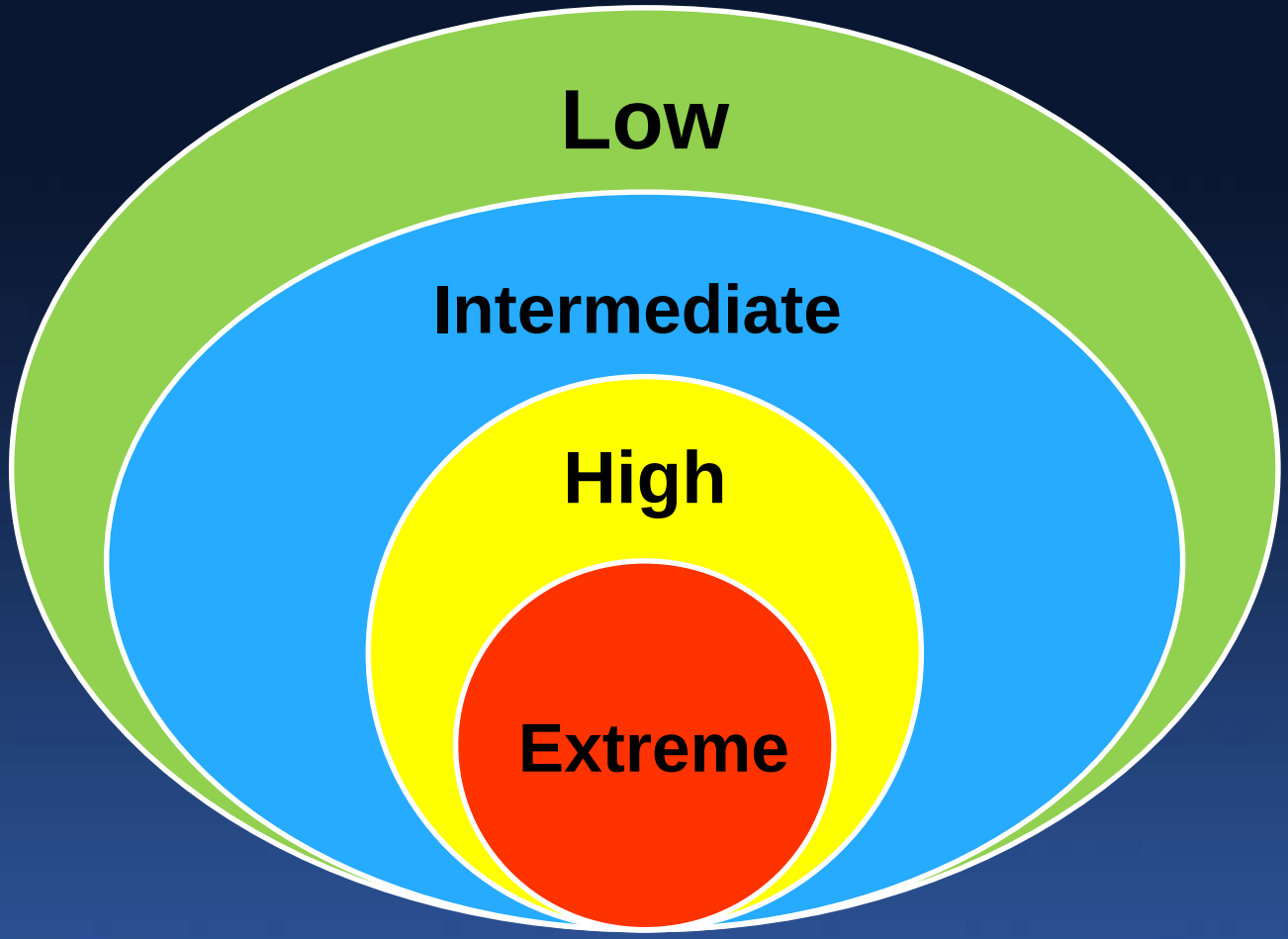
TAVR Landscape - 2018

Key Messages

- **The VARC initiative set the stage for PARTNER, which arguably became the most successful sequence of clinical trials EVER!**
- **The PARTNER trials and the MDT CoreValve studies applied the highest level of clinical trial rigor, including 8 RCTs, to validate the relative safety and efficacy of TAVR cw control therapies (e.g. medical Rx or surgery) in de-escalating risk strata over a ten-year period!**

TAVR Patient Selection

Surgical Risk Stratification

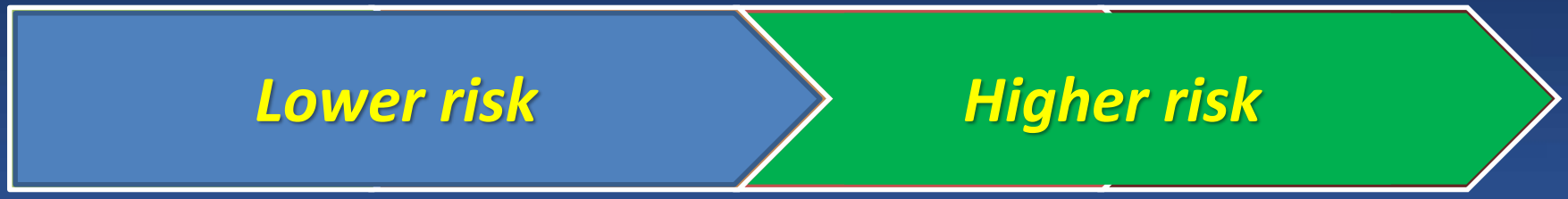


TAVR Risk Assessment

Risk Stratification Redefined

Traditional

Contemporary



TAVR Risk Assessment

TAVR Higher-Risk Strata

Futility (cohort C)

- Life expectancy < 1 year, despite successful TAVR
- Risk predictive models for early mortality or poor clinical outcomes with TAVR
- ⬆ co-morbidities (STS>15%)
- Frailty and dementia assessments critical
- *Rx = BAV or hospice*

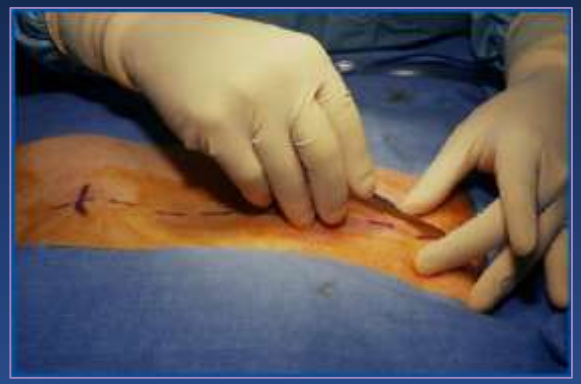
Role of Frailty Assessment

Robust

Frail

Extremely Frail
Debilitated

Frailty Syndrome



TAVR

Cachexia
Severe weakness
Wheelchair bound
Dementia
ADL dependencies

Hospice?
BAV?

Suzanne Arnold, TCT 2016

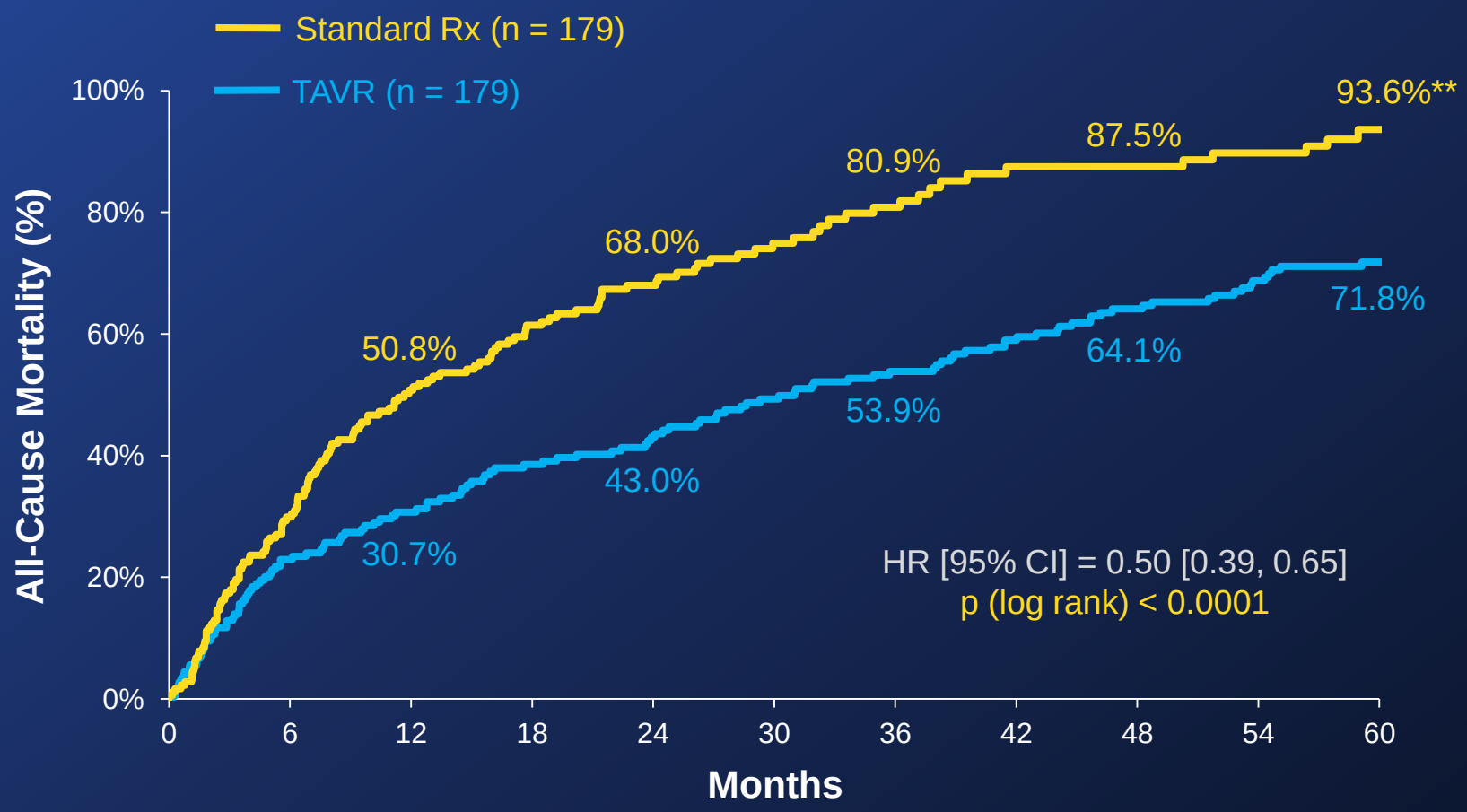
TAVR Risk Assessment

TAVR Higher-Risk Strata

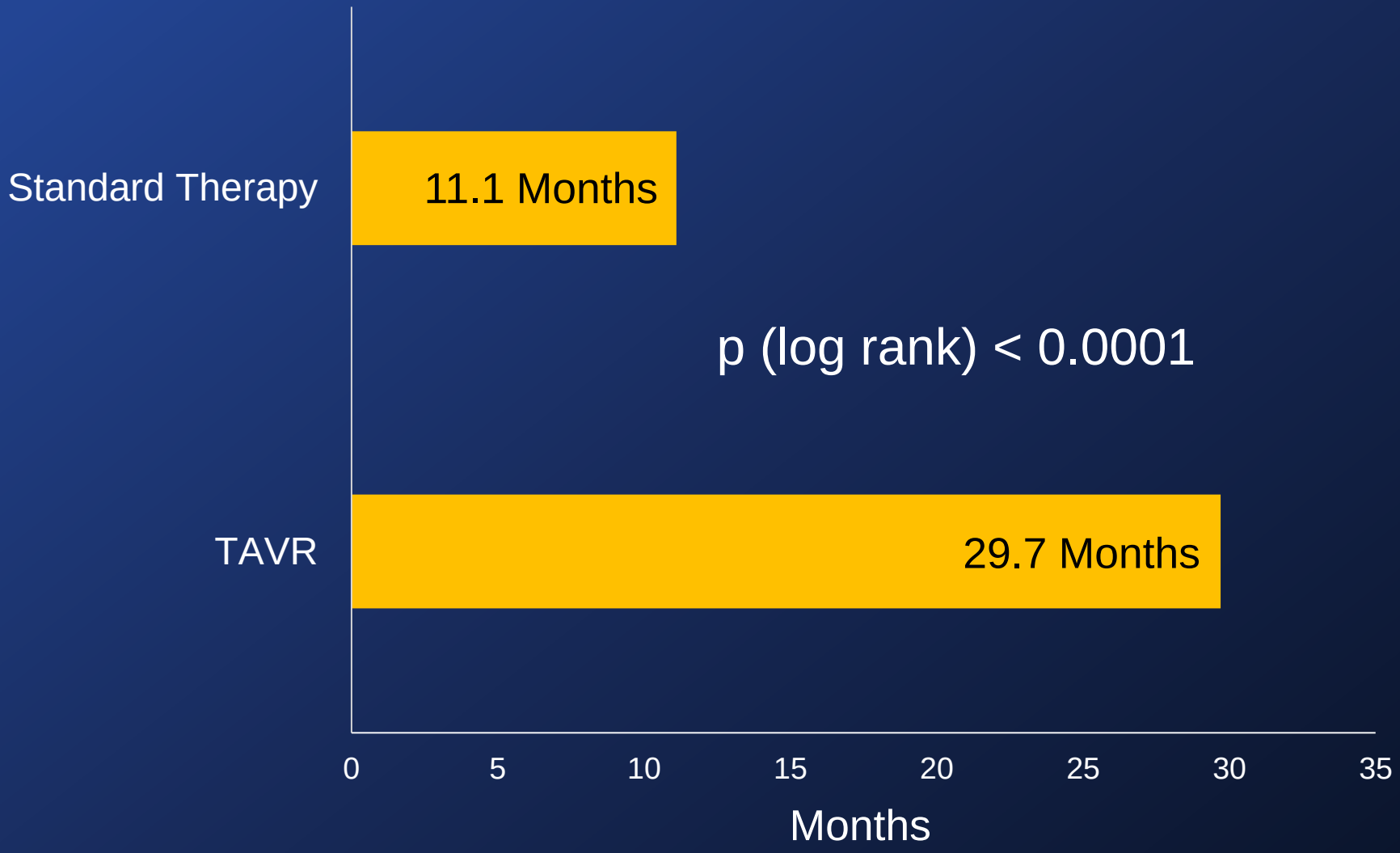
Extreme or Prohibitive Risk; "Inoperable"

- > 50% likelihood of death or irreversible morbidity
- Heart team decision with surgeons as the gatekeepers
- Clinical & anatomic exclusions for surgery
- *TAVR is only option*

All-Cause Mortality (ITT)
All Patients



All-Cause Mortality (ITT)
Median Survival



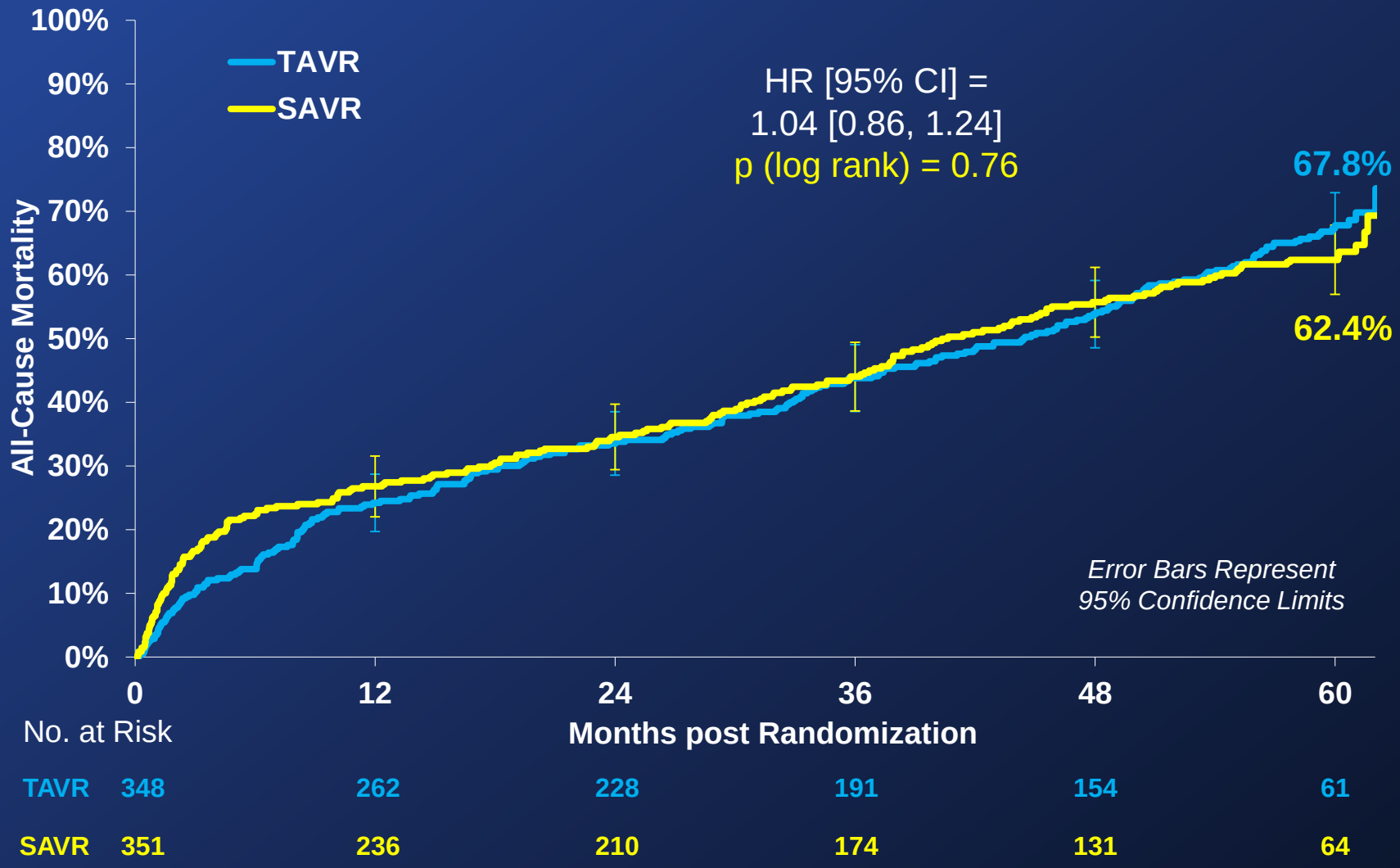
TAVR Risk Assessment

TAVR Higher-Risk Strata

High Risk

- STS score ≥8%
- Combination of clinical co-morbidities and anatomic factors
- Requires surgical input and Heart Team
- *Unless negative anatomic factors, TAVR preferred*

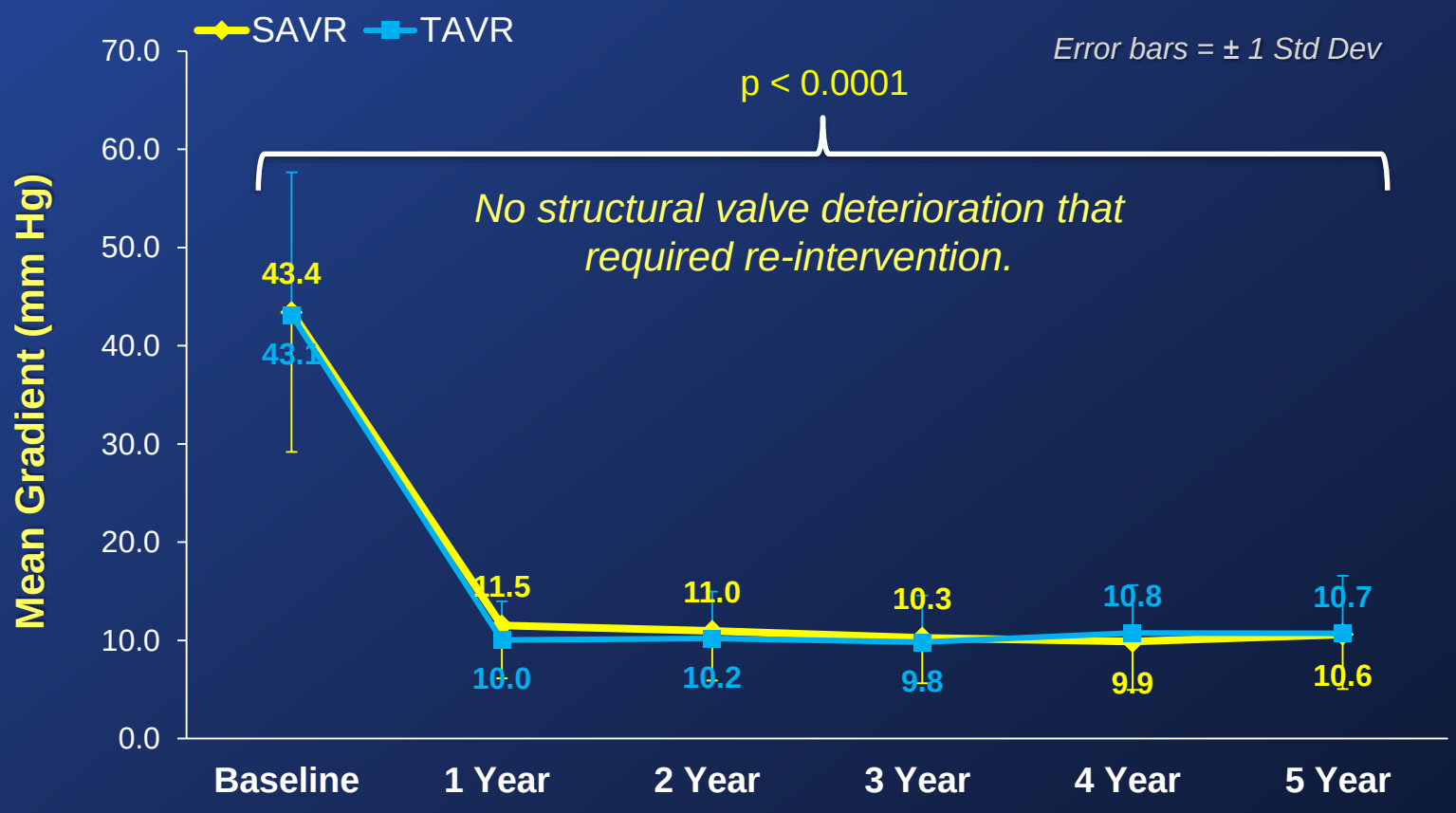
All-Cause Mortality (ITT)
All Patients



No. at Risk

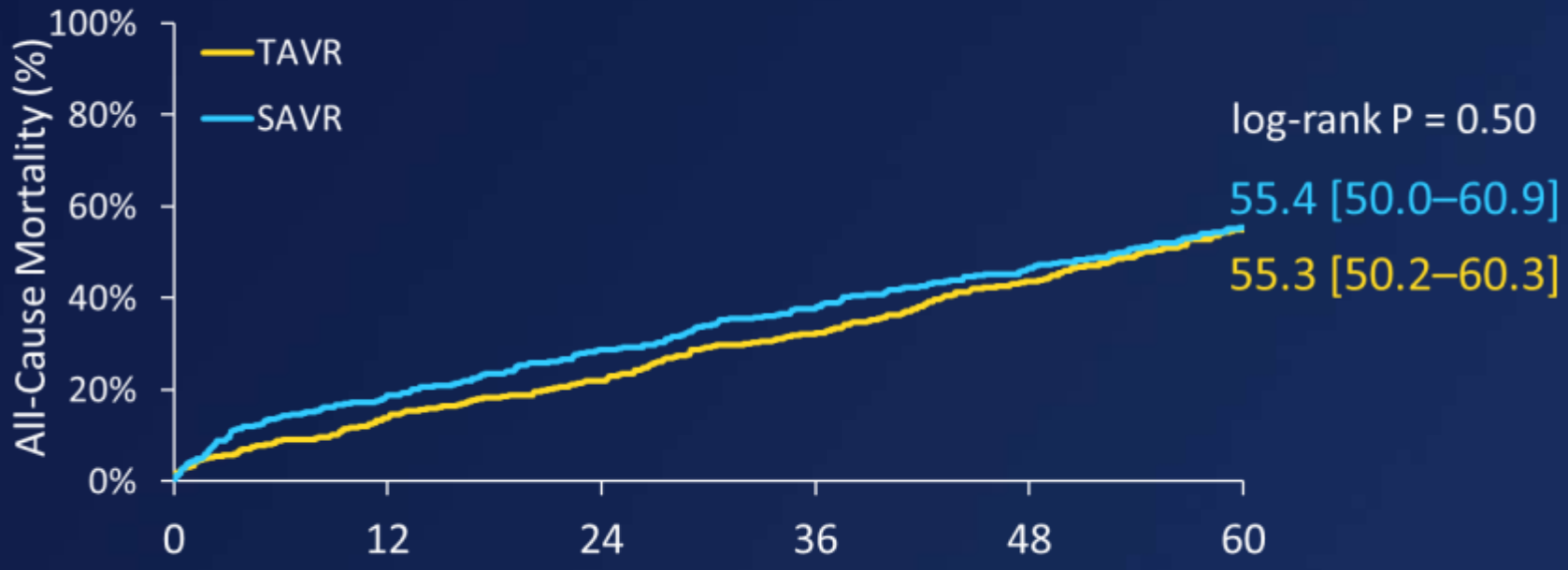
TAVR	348	262	228	191	154	61
SAVR	351	236	210	174	131	64

Aortic Valve Mean Gradient



	Baseline	1 Year	2 Year	3 Year	4 Year	5 Year
TAVR	310	219	156	106	79	56
SAVR	299	158	123	86	61	48

All-Cause Mortality



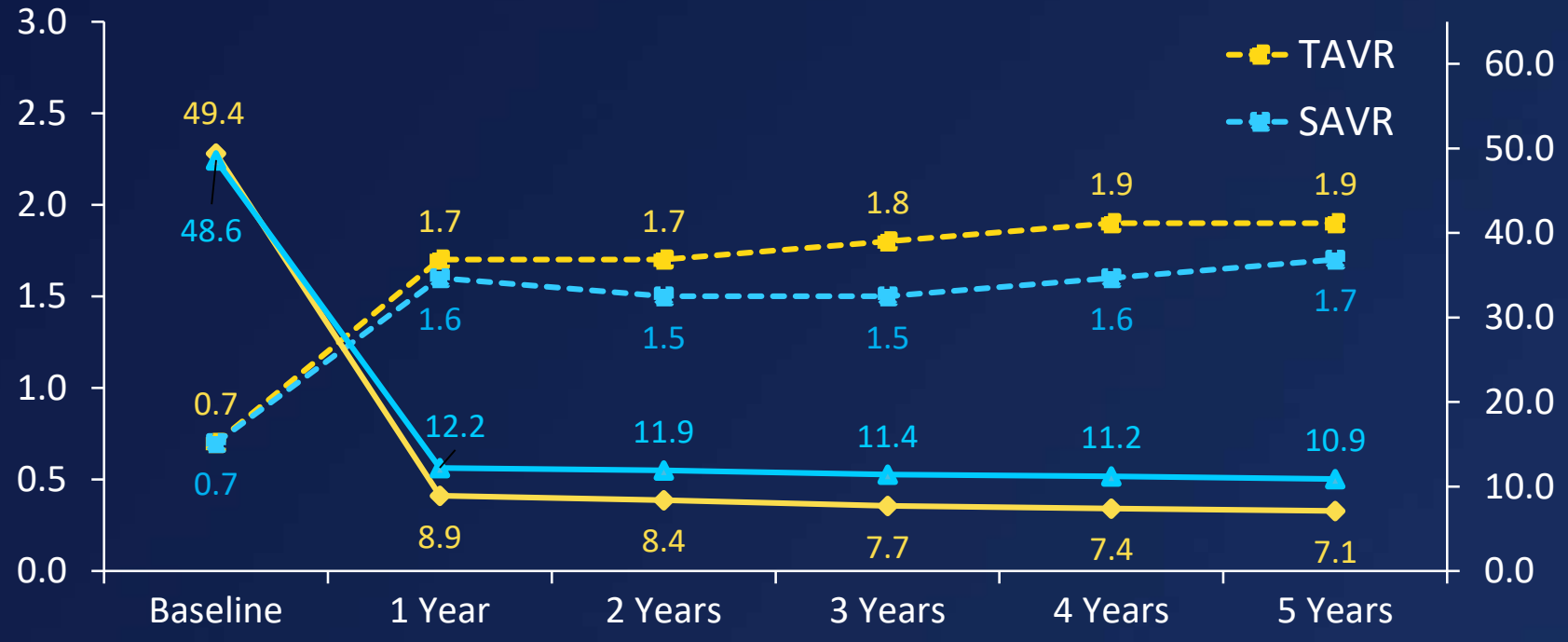
No. at risk

TAVR	391	336	301	253	205	135
SAVR	359	284	241	199	162	101

[95% confidence intervals]

Valve Hemodynamics

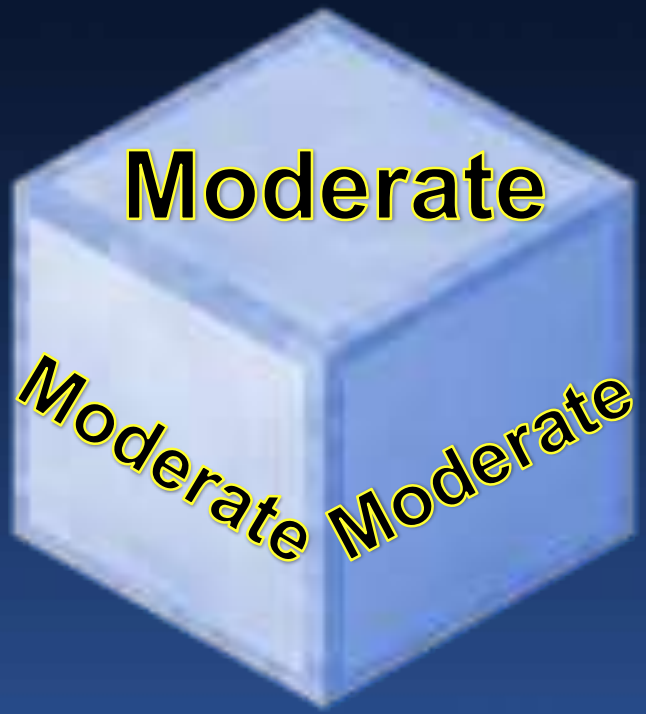
P < 0.01 for TAVR vs. SAVR at all follow-up time points



TAVR AVG	391	303	250	193	152	112
SAVR AVG	359	230	188	141	114	88
TAVR EOA	384	284	238	182	144	99
SAVR EOA	353	210	174	134	106	84

TAVR Risk Assessment

TAVR Lower-Risk Strata

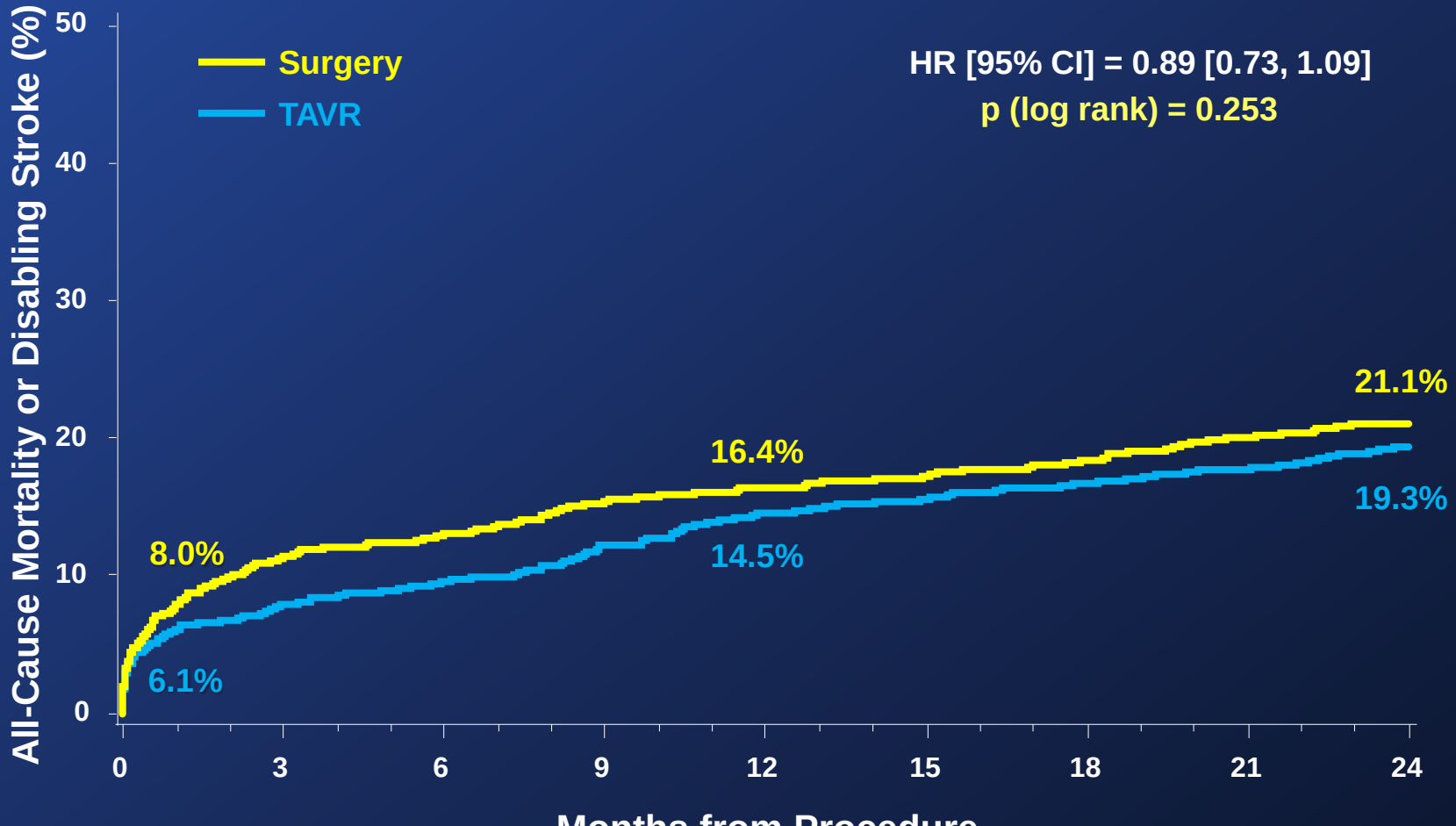


Moderate risk = Intermediate risk

- STS ≈ 3 – 8%
- Mean age ≈ 80 yo
- Clearly surgical candidates
- *Choice of TAVR vs. surgery based on clinical/ anatomic factors and patient preference*

Primary Endpoint (ITT)
All-Cause Mortality or Disabling Stroke

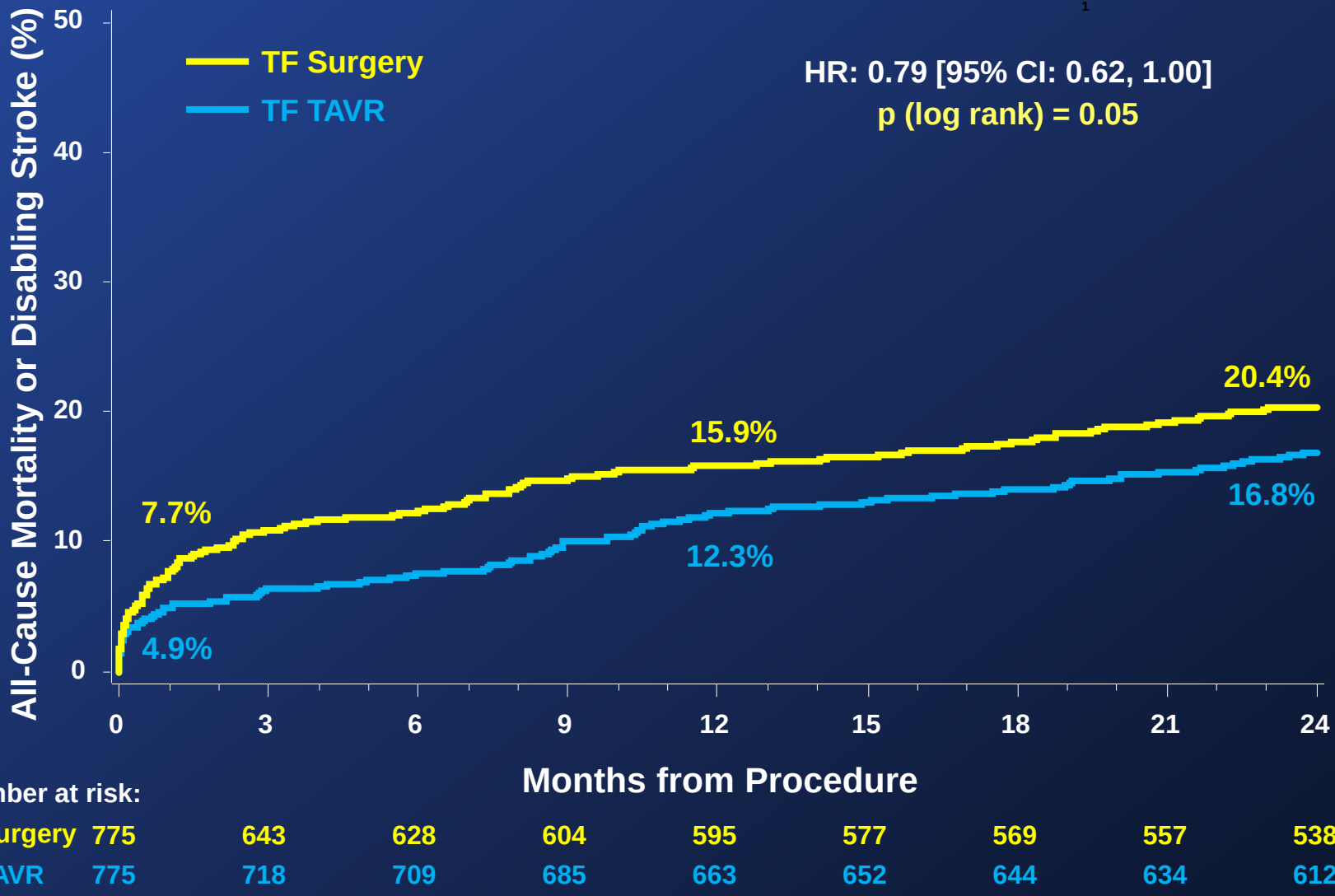
THE PARTNER II TRIAL



Number at risk:									
Surgery	1021	838	812	783	770	747	735	717	695
TAVR	1011	918	901	870	842	825	811	801	774

TF Primary Endpoint (ITT)
All-cause Mortality or Disabling Stroke

THE PARTNER II TRIAL



Number at risk:									
TF Surgery	775	643	628	604	595	577	569	557	538
TF TAVR	775	718	709	685	663	652	644	634	612

P2A and S3i Perspectives
Key findings

THE PARTNER II TRIAL

Surgery better

Vascular complications
PVR

TAVR better

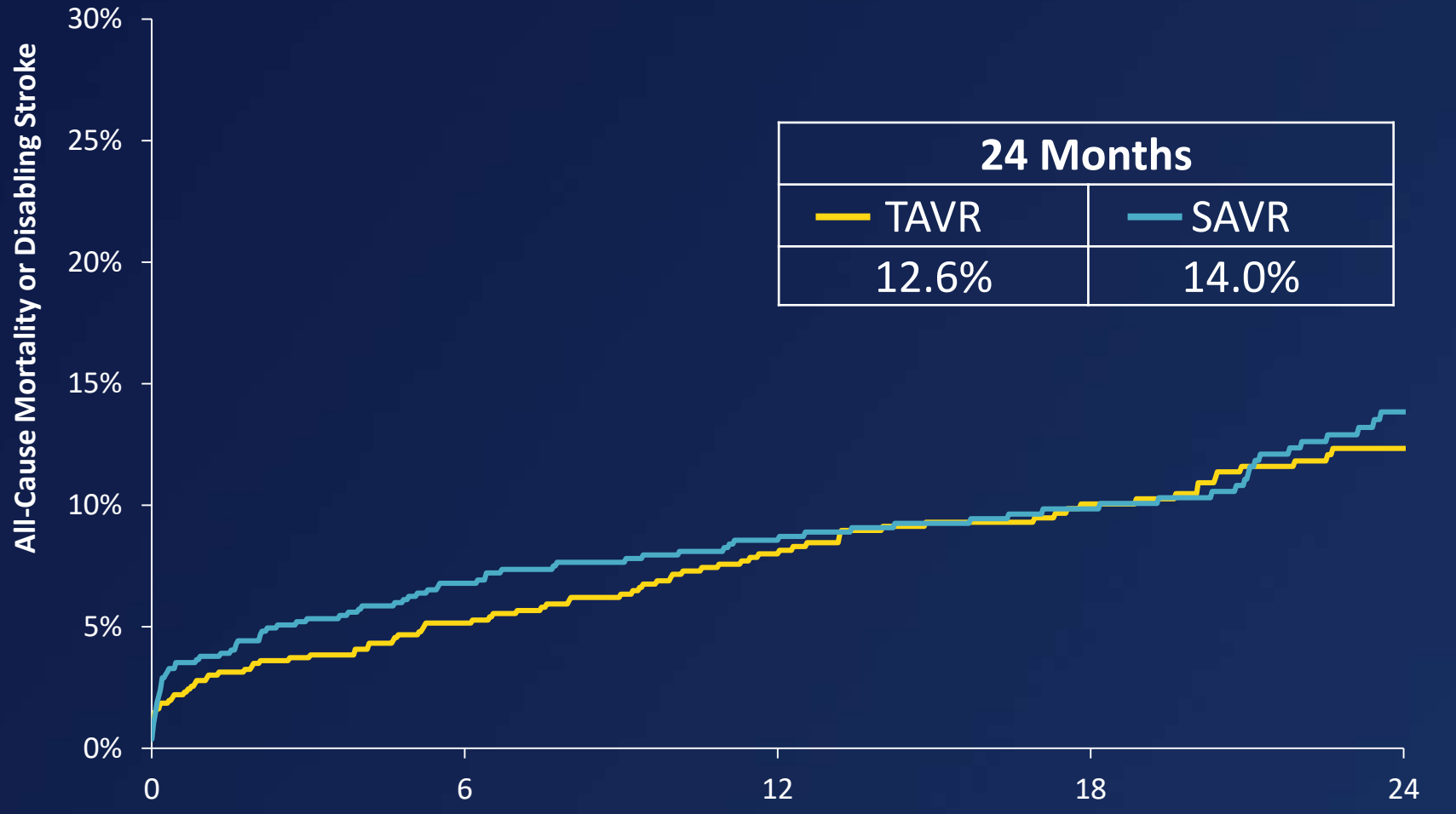
Mortality
Strokes
AKI
Severe bleeding
New onset AF
Valve area
30-day QOL
30-day 6MWT
ICU/hospital LOS
Days alive OOH

Which therapy do you think is better?

SURTAVI Trial

CoreValve SURTAVI Trial

All-Cause Mortality or Disabling Stroke

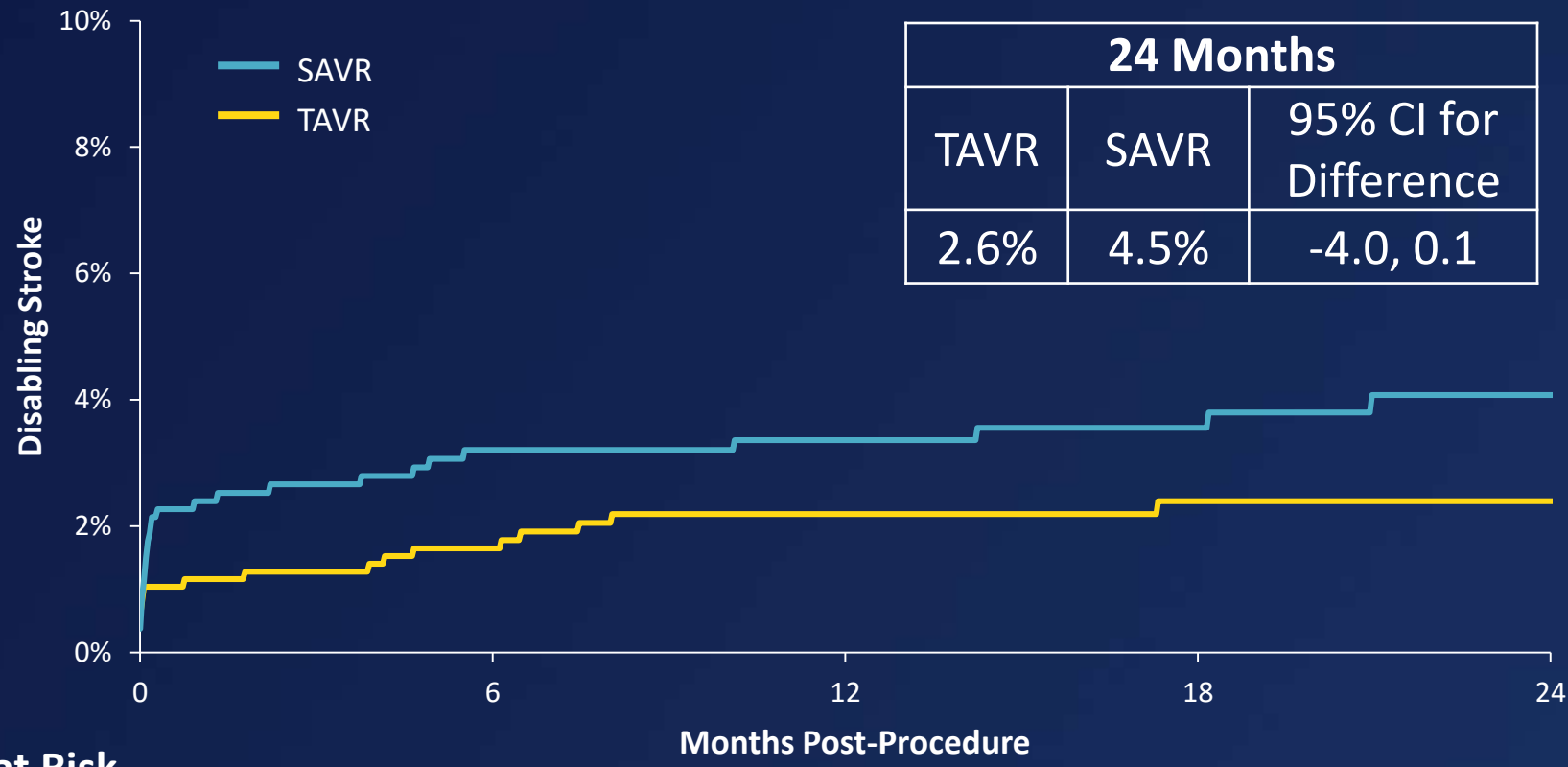


24 Months	
TAVR	SAVR
12.6%	14.0%

No. at Risk					
SAVR	796	674	555	407	241
TAVR	864	755	612	456	272

SURTAVI Trial

Disabling Stroke



24 Months		
TAVR	SAVR	95% CI for Difference
2.6%	4.5%	-4.0, 0.1

No. at Risk

SAVR	796	674	555	407	241
TAVR	864	755	612	456	272

TAVR Guidelines

The "New" AHA/ACC Focused Update

2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Severe AS
Symptomatic

Surgical Risk Strata

Low	Intermediate	High	Prohibitive
SAVR	***SAVR or TAVR***	***SAVR or TAVR***	***TAVR***
IB	IIa B	IA	IA

TAVR Guidelines

The "New" ESC/EACTS VHD Report

2017 ESC/EACTS Guidelines for the management of valvular heart disease

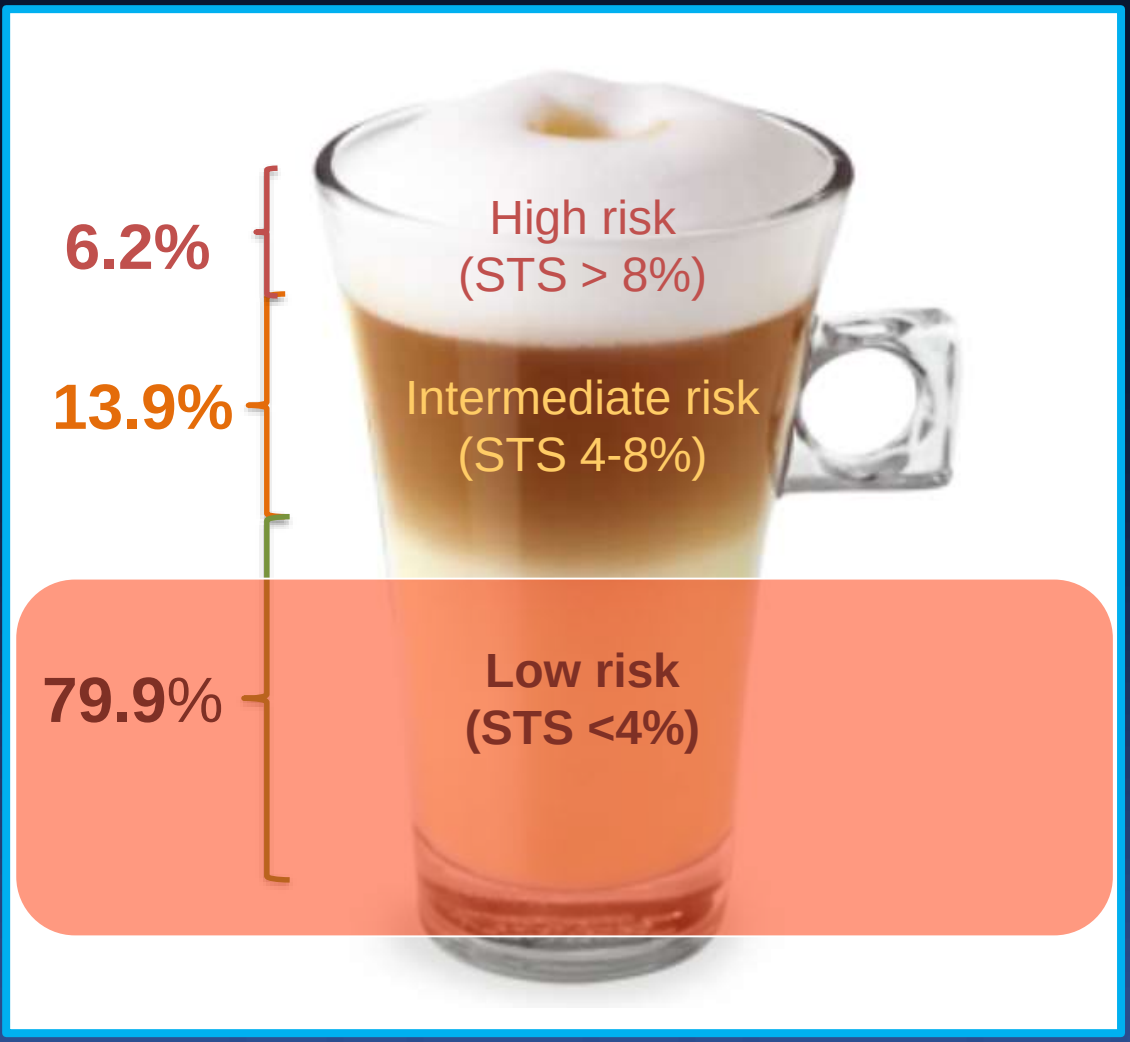
The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Severe AS
Symptomatic

Surgical Risk Strata

Low	Intermediate or High	Prohibitive
SAVR	***SAVR or TAVR***	***TAVR***
IB	IB	IB

STS database 2002-2010 *(141,905 pts)*

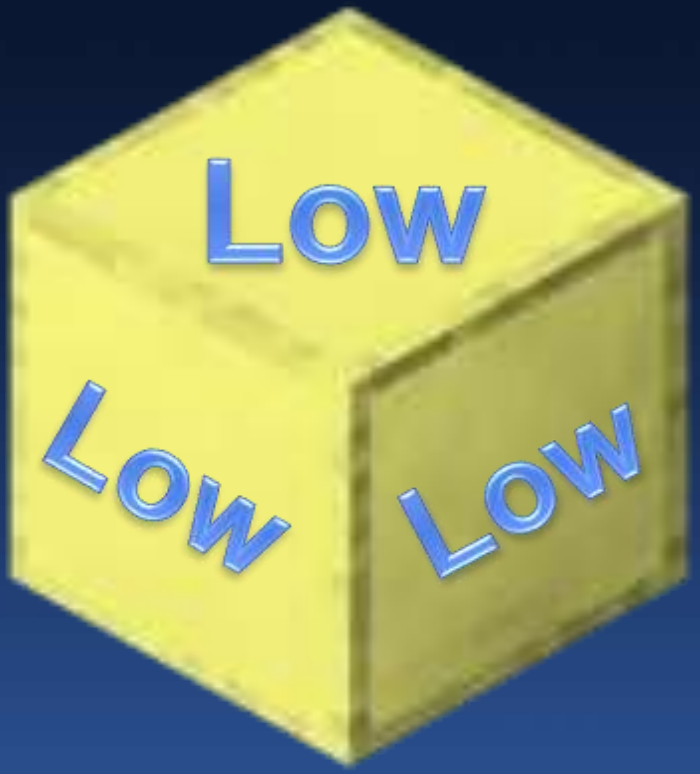


The 'holy grail'
80% low-risk
AS patients!

Courtesy of N. Piazza, V. Thourani

TAVR Risk Assessment

TAVR Lower-Risk Strata



Low risk

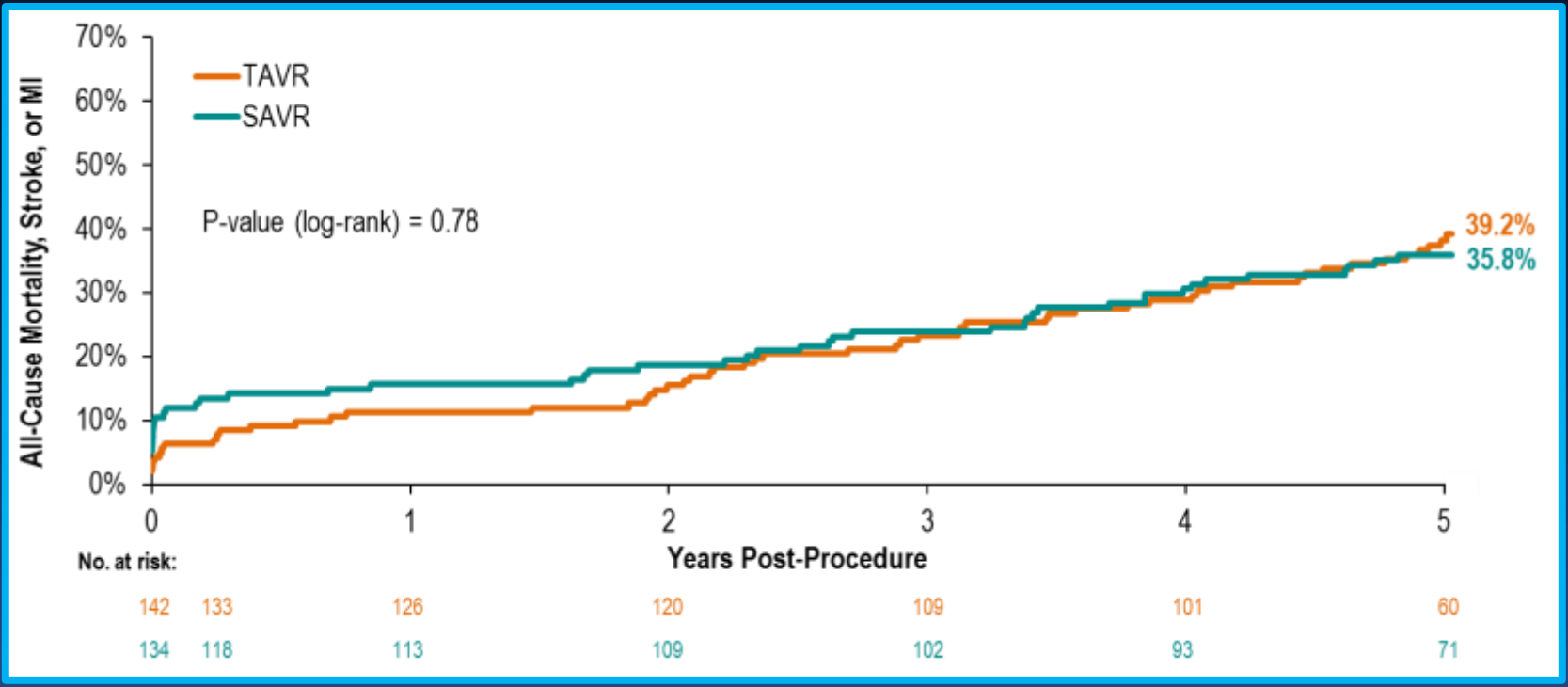
- STS < 3%
- Mean age ≈ 65-80 yo
- Usual surgical patient!
- Subset of bicuspid AV
- Limited clinical data, BUT 4 major RCTS ongoing – data in 2019!
- *Will certainly involve a "shared" decision-making process*

NOTION: Baseline Characteristics

Characteristic, % or mean ± SD	TAVR n=145	SAVR n=135	*P* value
Age (yrs)	79.2 ± 4.9	79.0 ± 4.7	0.71
Male	53.8	52.6	0.84
Society of Thoracic Surgeons (STS) Score	2.9 ± 1.6	3.1 ± 1.7	0.30
STS Score < 4%	83.4	80.0	0.46
Logistic EuroSCORE I	8.4 ± 4.0	8.9 ± 5.5	0.38
NYHA class III or IV	48.6	45.5	0.61

NOTION: Death (all-cause), Stroke or MI at 5 Years (as-treated)

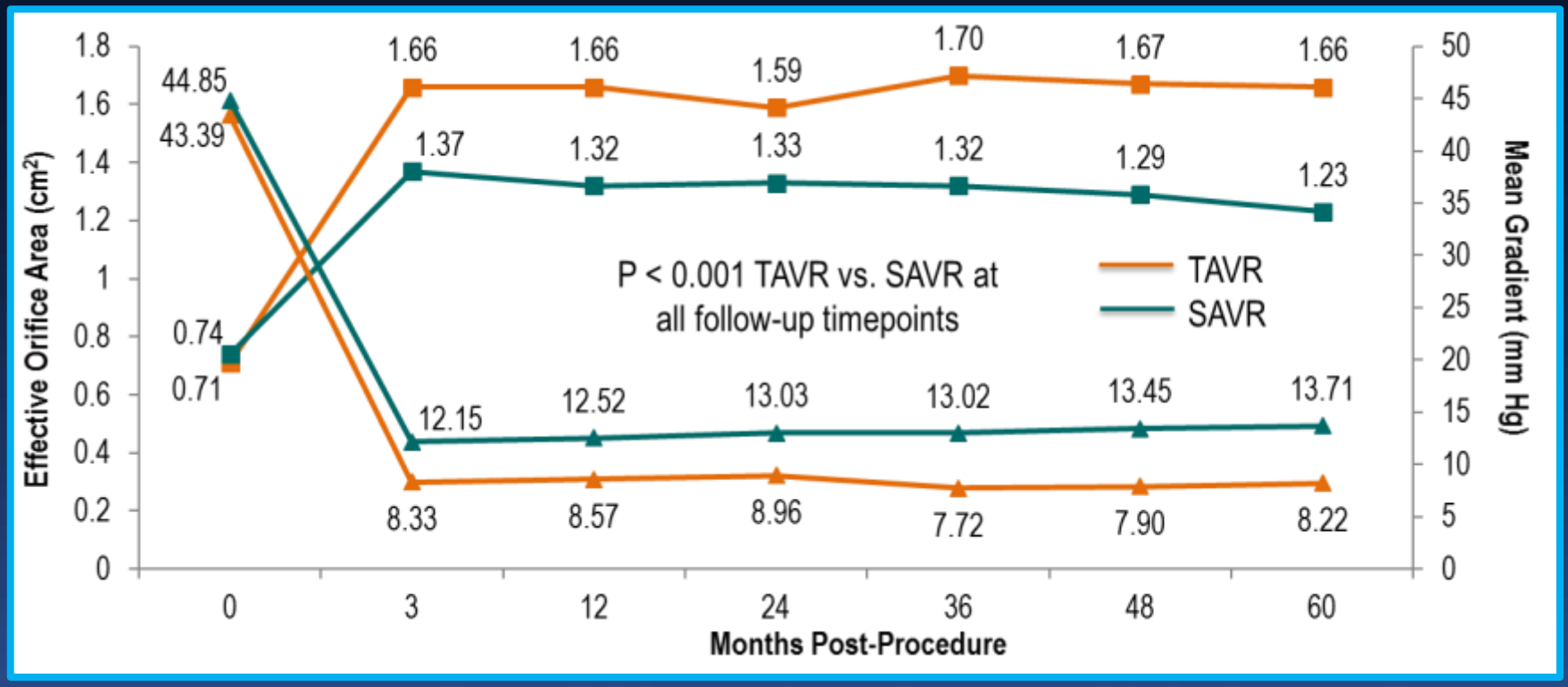
CoreValve vs. Surgery in Low-Risk Patients (N = 280)



PIs: H. Gustav Hørsted Thyregod and Lars Sondergaard,

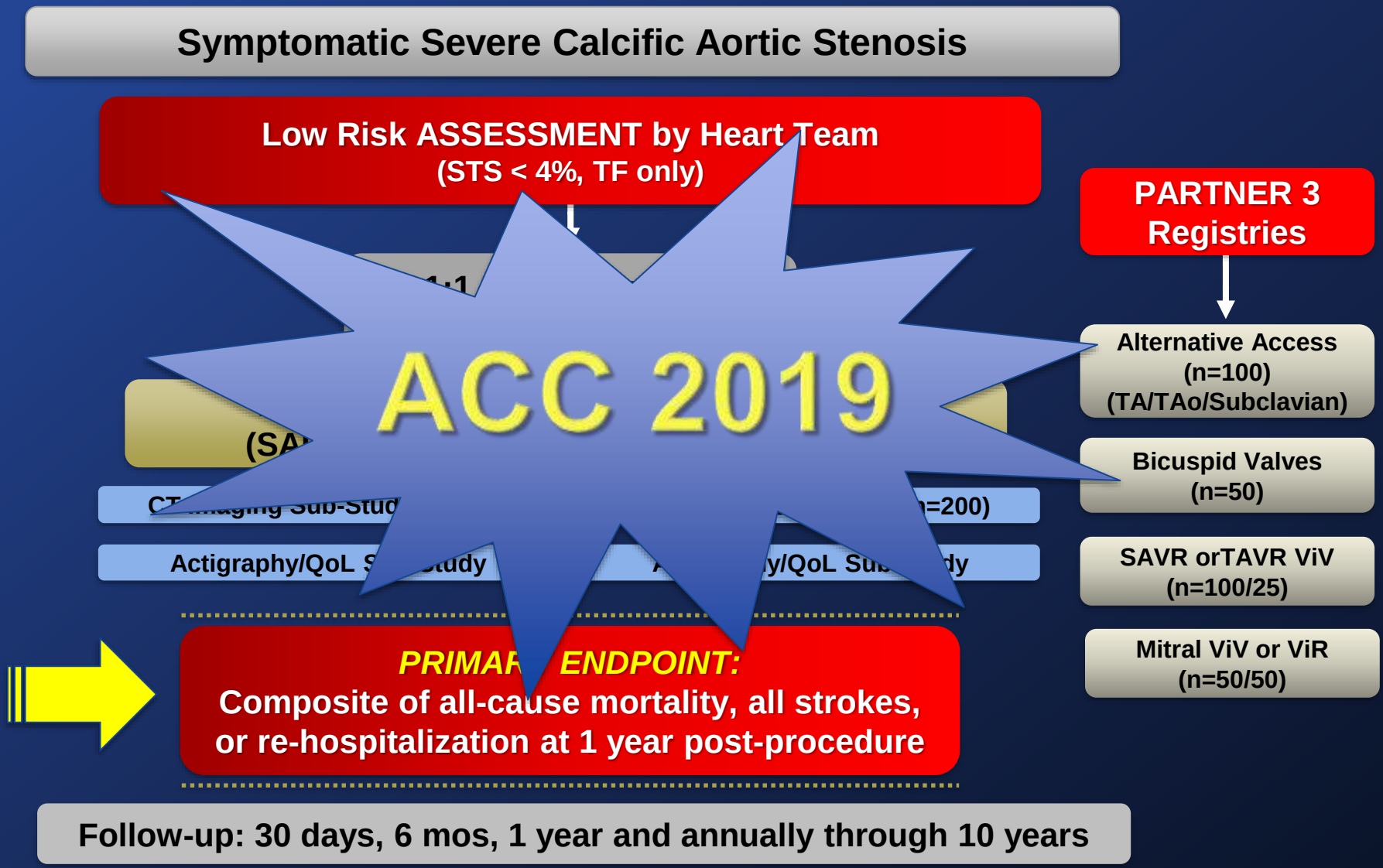
NOTION: Valve Performance (echo) thru 5 years (as treated)

CoreValve vs. Surgery in Low-Risk Patients (N = 280)



PIs: H. Gustav Hørsted Thyregod and Lars Sondergaard,

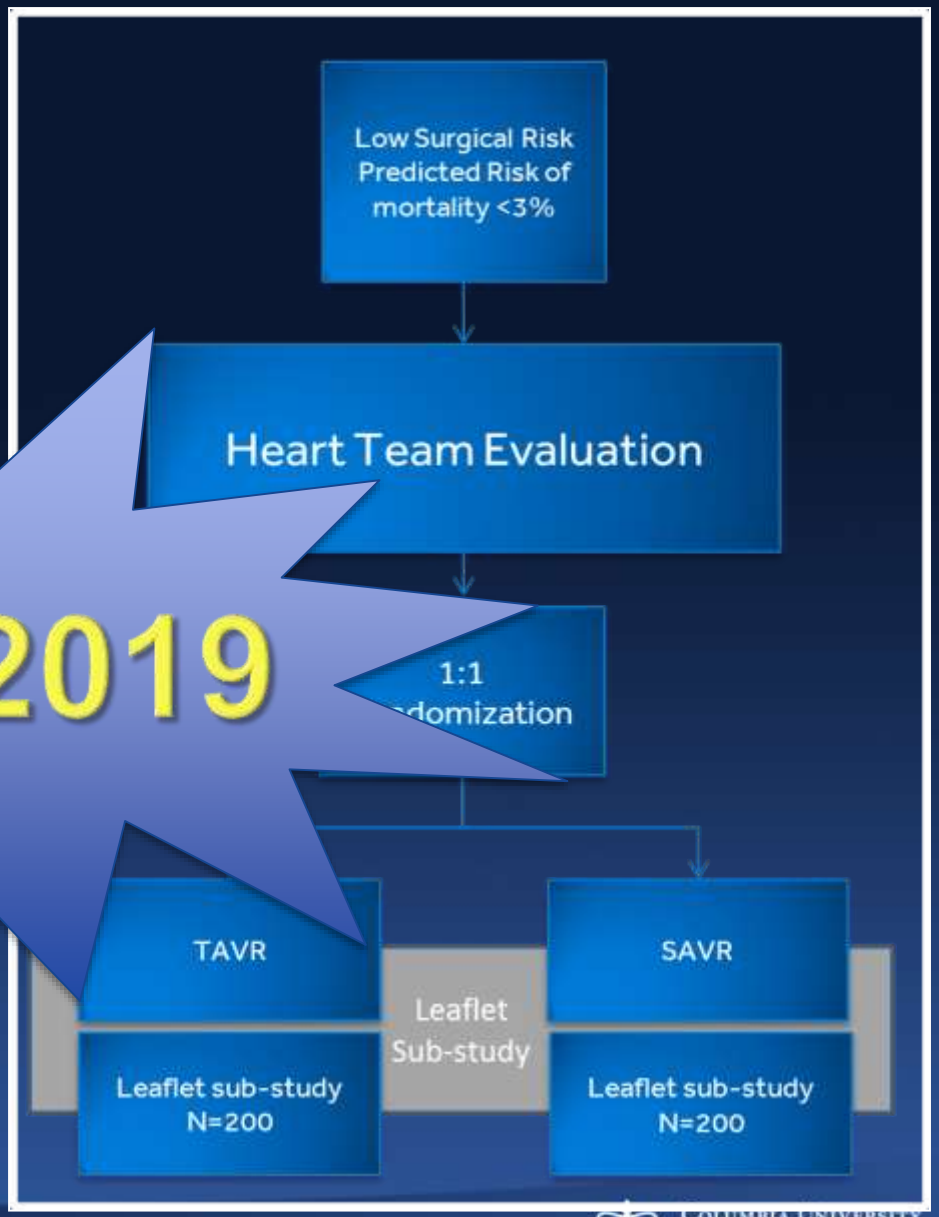
The PARTNER 3 Trial
Study Design



MEDTRONIC TAVR RCT IN LOW RISK PATIENTS

TRIAL DESIGN & LEAFLET SUB-STUDY

- **Patient Population: Low Risk Cohort**
  - Determined by Heart Team to be low surgical risk
- **Primary Endp int:**
  - Safety: Death, all s life-threateni ding, major vascular compli AKI at 30 days
  - Efficacy: Death o
- **Sample Size: ~12**
- **Follow-up Evaluations:**
  - 30-days, 6-month , 18-month, and 1 thru 5 rs
- **Number of Sites: Up to 80 sites**



ACC 2019

Who should receive TAVR?

Who does not deserve surgery?

Columbia University Medical Center
NewYork-Presbyterian

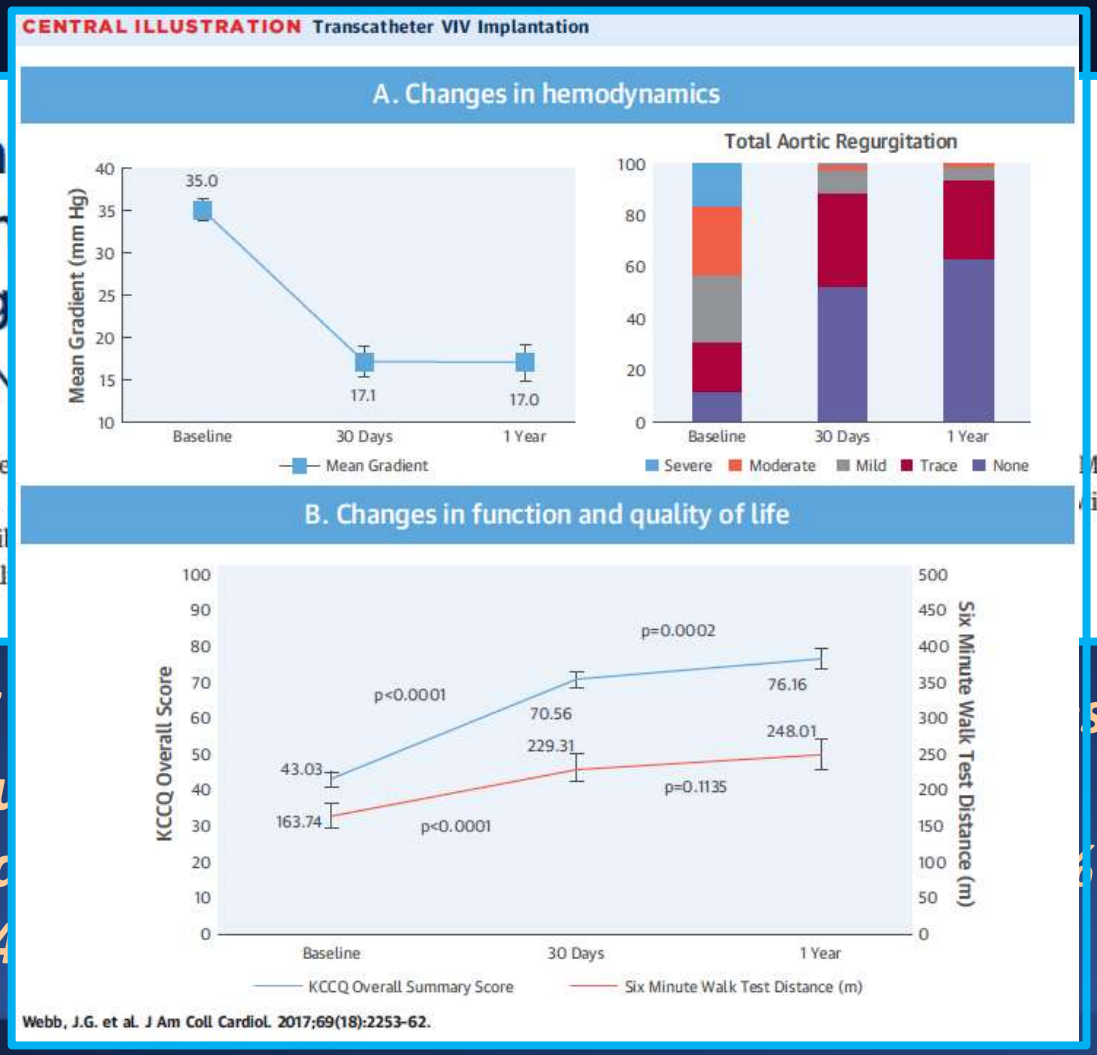
TAVR Landscape - 2018

Key Messages

- **Along the TAVR journey, we studied important TAVR subgroups and aspects of bioprosthetic valve function, patient responses to therapy, and socio-economic impact.**

TAVR for Bioprosthetic Valve Failure

Valve-in-Valve



- *365*
- *30-d*

sis

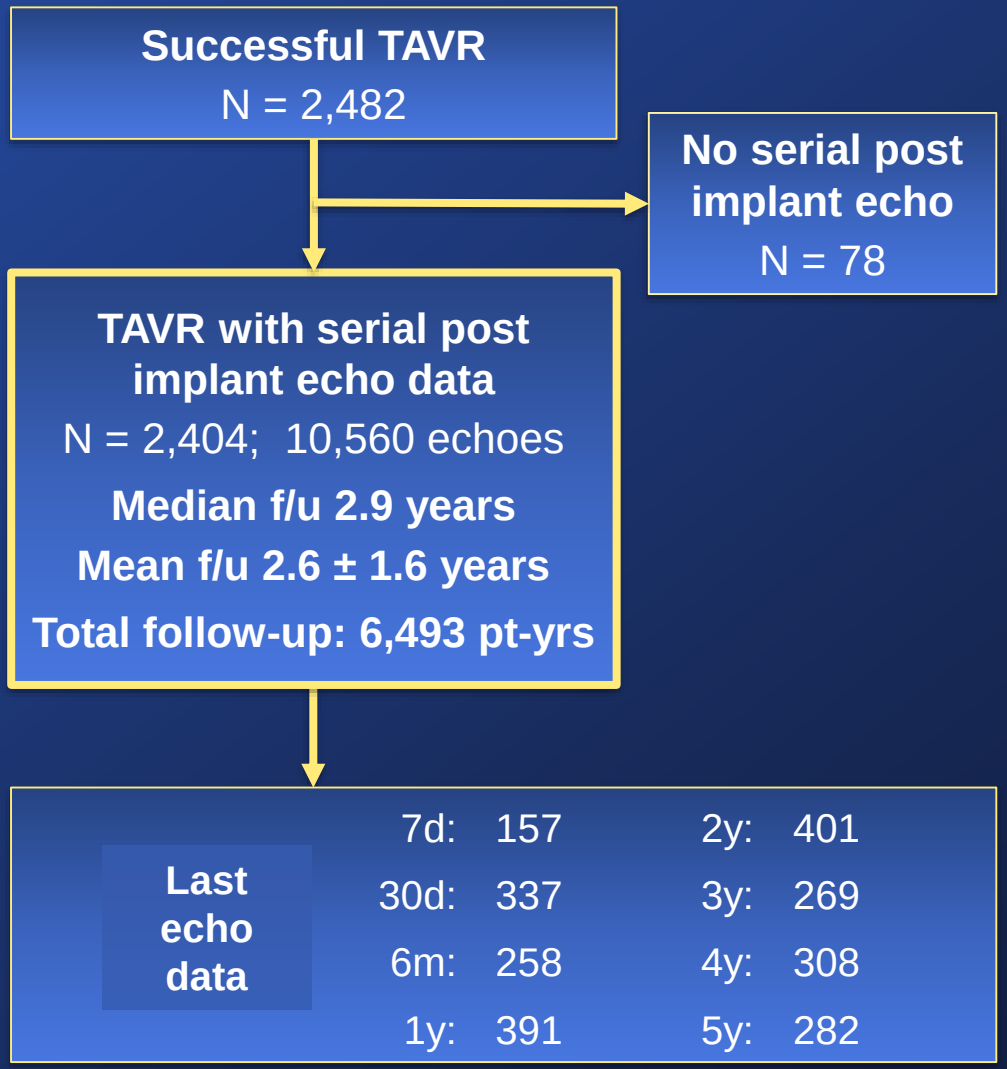
failu

and

12.4

Webb JG et al. JACC 2017;69:2253-62

Cohort Derivation and Characteristics



Population characteristics

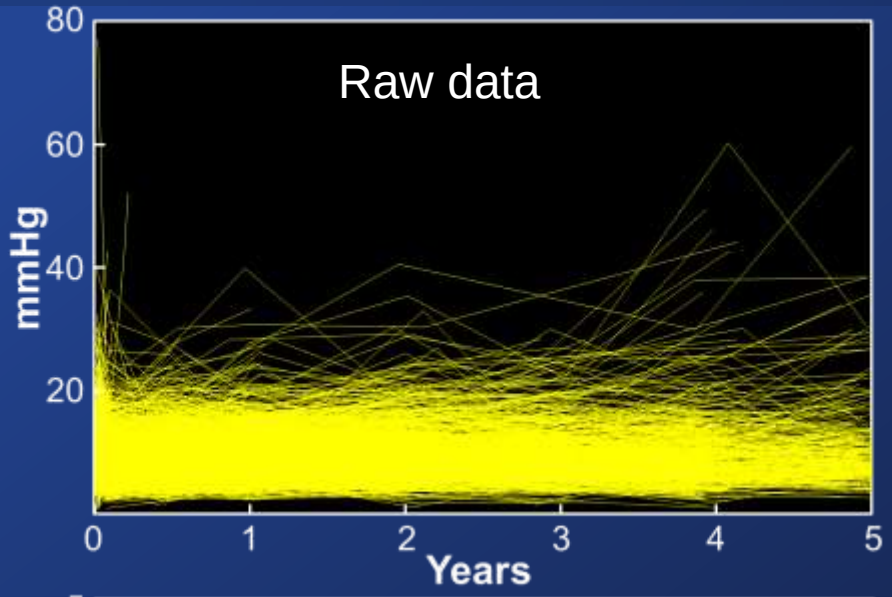
- Mean age 84.5 yrs
- 48% female
- 95% NYHA class 3-4
- 92% obstructive CAD
- Severe AS: AVA 0.65 cm^2

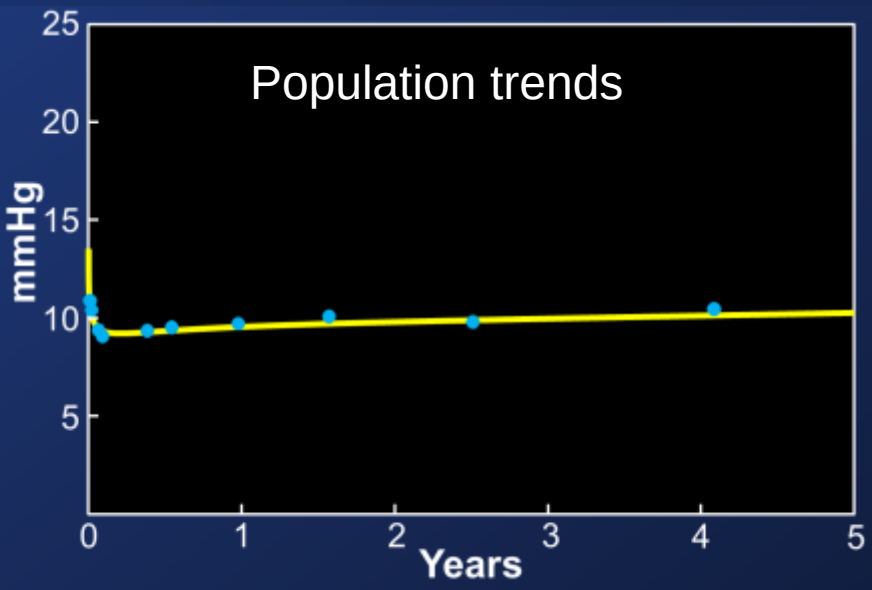
- THV size: 52% 23; 48% 26
- Access: 43% TA ; 57% TF

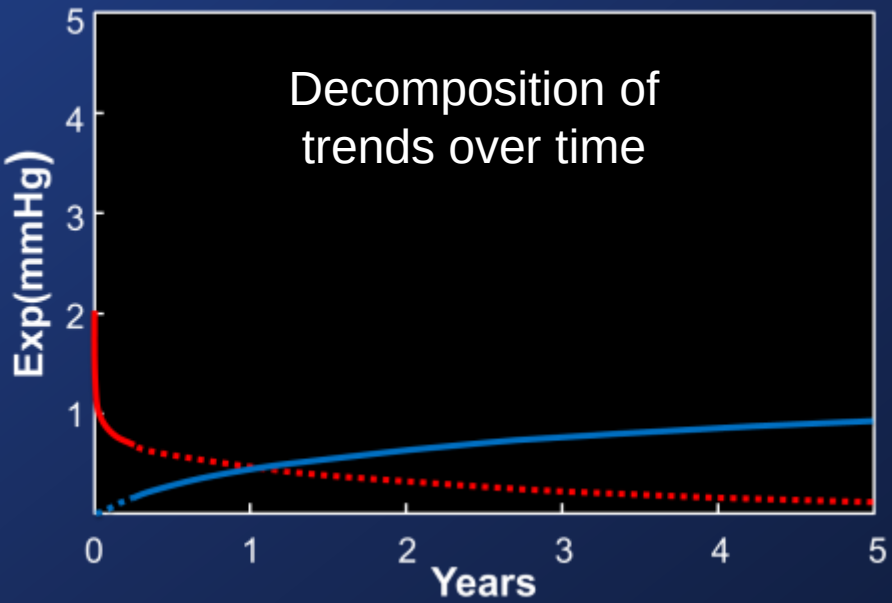
Survival w/o reintervention

- 39% at 5 years by non-adjusted parametric estimate

AV Mean Gradient Population Trends: Early Post Implant and Midterm to 5 Yrs



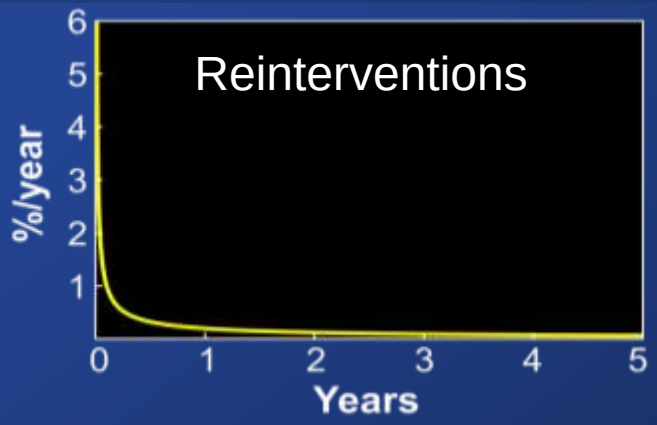




Early change:
12.1 to 9.2 mmHg

Late change:
9.2 to 10.3 mmHg
Slope: 0.0018± 0.0039

AV Reintervention: Incidence and Case Reviews

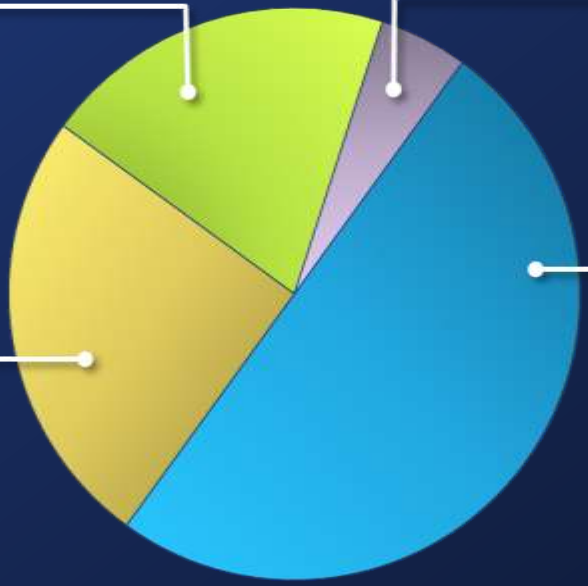


- **20 pts with reintervention**
  (9 SAVR, 8 late valve-in-valve, 3 BAV)
- **Indication: Structural cause in 5 (25%)**
  AS: n=1; Valve thrombosis: n=1; Trans AR: n=3

20 pts with reintervention

Adverse Changes
(N = 4, 20%)
Classic ↑ gradient, ↓ EOA, ↓ DVI

Adverse Initial
(N = 1, 5%)
High initial gradient, no change

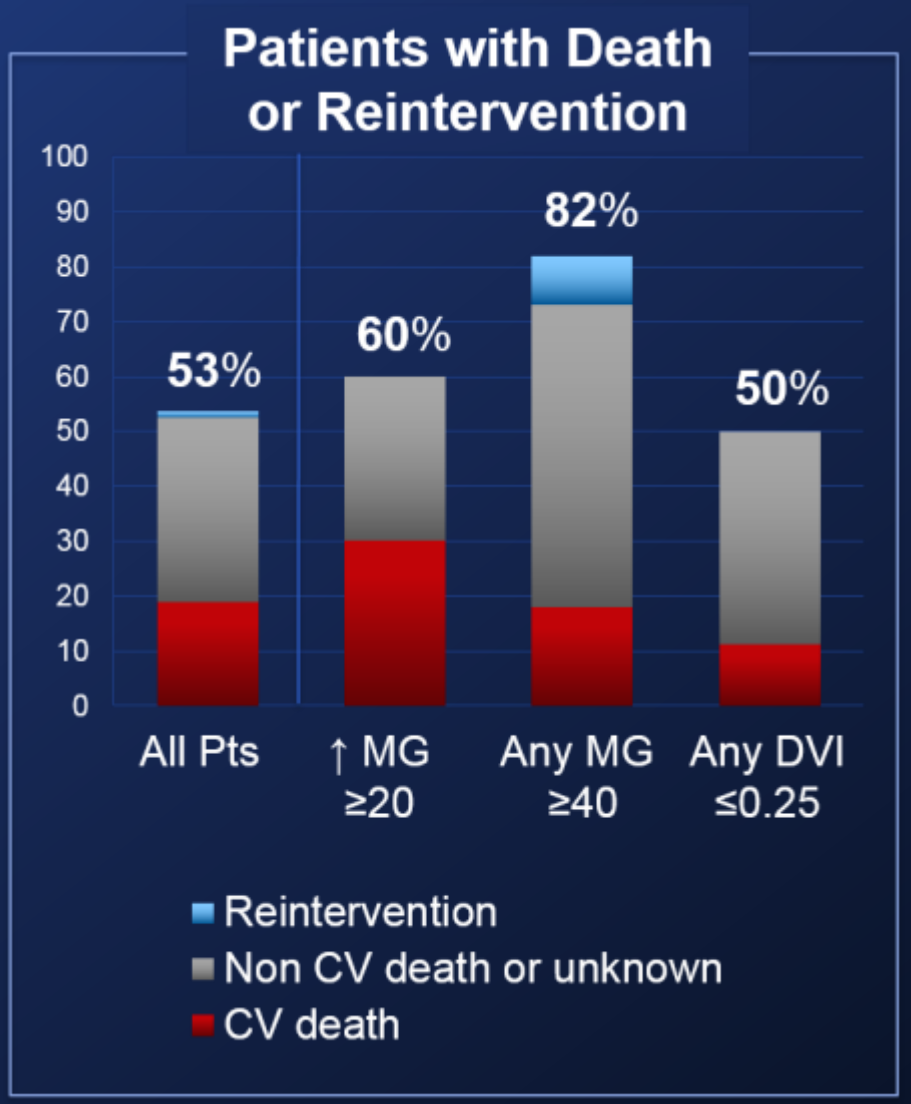


No Changes
(N = 10, 50%)
- No appreciable or consistent hemodynamic changes
- Last echo data > 1 mo prior to reintervention in 9/10 pts

No Data
(N = 5, 25%)
No post-implant trial echo data

Valve Safety: Case Reviews of Hemodynamic 'Outliers'

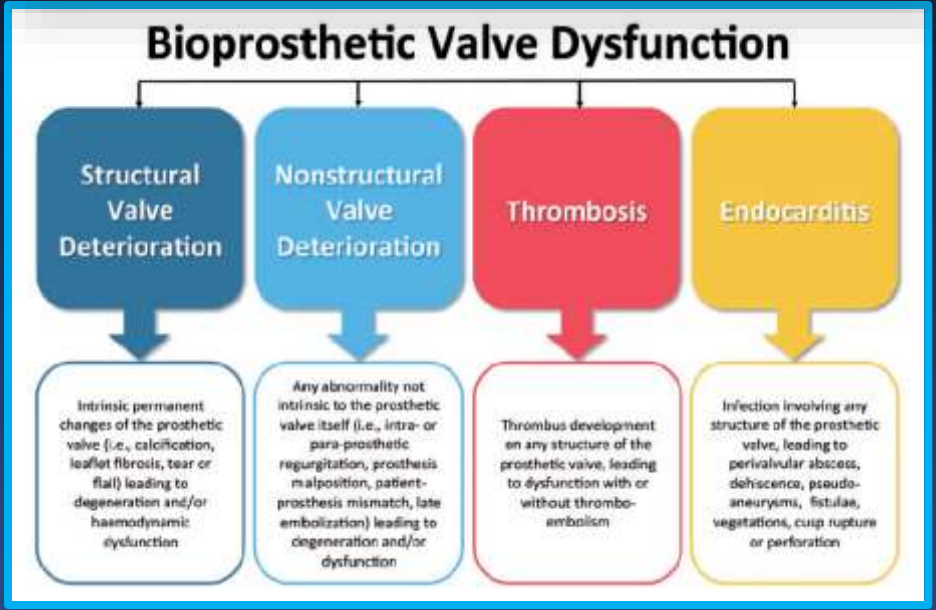
- VARC-2 ID'd 'mild AS' in 3-48%
  - Similar rates in SAVR and TAVR
  - Impractical for case review
- ↑ AV mean gradient ≥ 20 mmHg
  - N=10 (0.45%)
  - 6 deaths (3 CV), no reintervention
- Any mean gradient ≥ 40 mmHg
  - N=11 (0.46%)
  - 8 deaths (2 CV), 1 reintervention
- Any DVI ≤ 0.25
  - N=44 (1.8%)
  - 22 deaths (5 CV), no reintervention

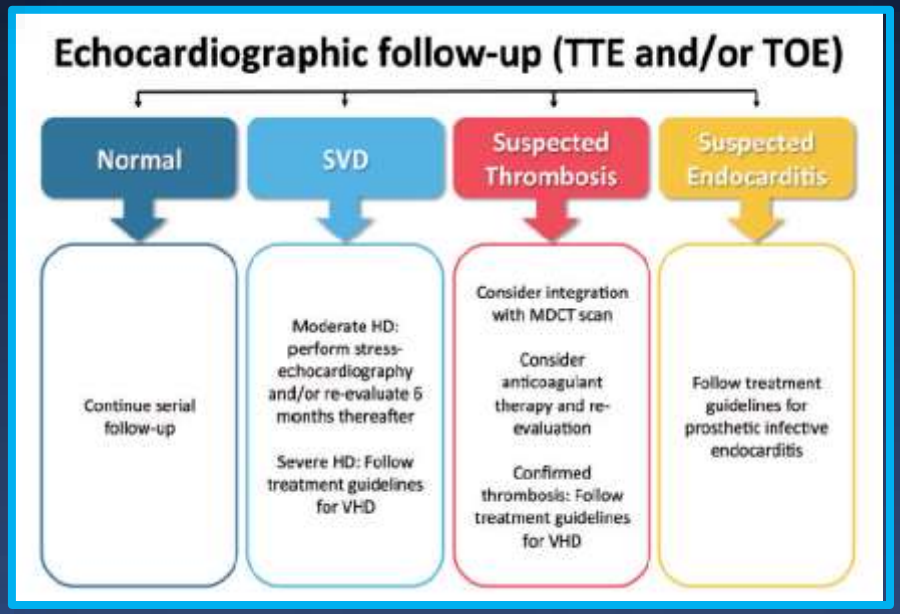


Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Davide Capodanno[1*†], Anna S. Petronio[2†], Bernard Prendergast[3], Helene Eltchaninoff[4], Alec Vahanian[5], Thomas Modine[6], Patrizio Lancellotti[7], Lars Sondergaard[8], Peter F. Ludman[9], Corrado Tamburino[1], Nicolò Piazza[10], Jane Hancock[3], Julinda Mehilli[11], Robert A. Byrne[12], Andreas Baumbach[13], Arie Pieter Kappetein[14], Stephan Windecker[15], Jeroen Bax[16], and Michael Haude[17]

New EU guidance with standardized definitions and endpoints to assess bioprosthetic aortic valve deterioration and failure



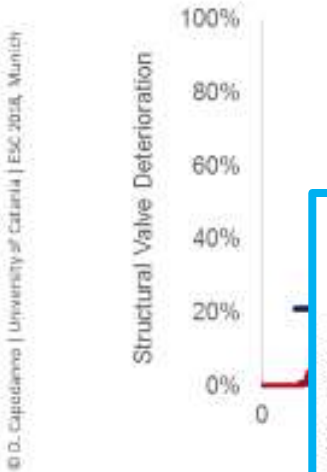


Capodanno D et al. Europ Heart J 2017

Head-to-Head Durability of TAVI vs SAVR

6-Year Outcomes of the NOTION Trial

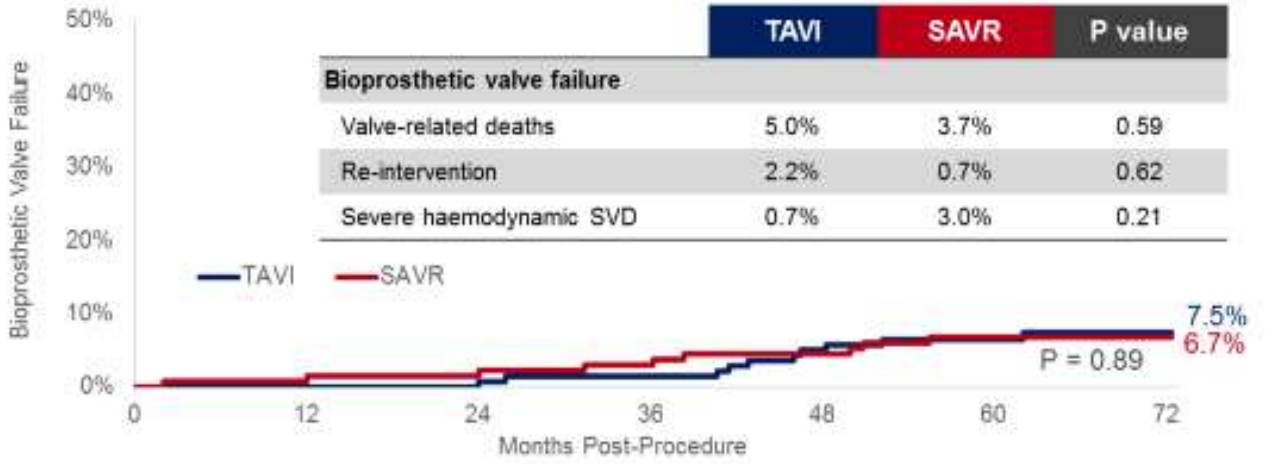
NOTION: 280 patients at low surgical risk randomized to TAVI or SAVR | Structural Valve Deterioration



	TAVI	SAVR
Structural valve deterioration		
Moderate haemodynamic SVD	3.6%	23.7%
Severe haemodynamic SVD	0.7%	3.0%

ESC Congress Munich 2018

NOTION: 280 patients at low surgical risk randomized to TAVI or SAVR | Bioprosthetic Valve Failure



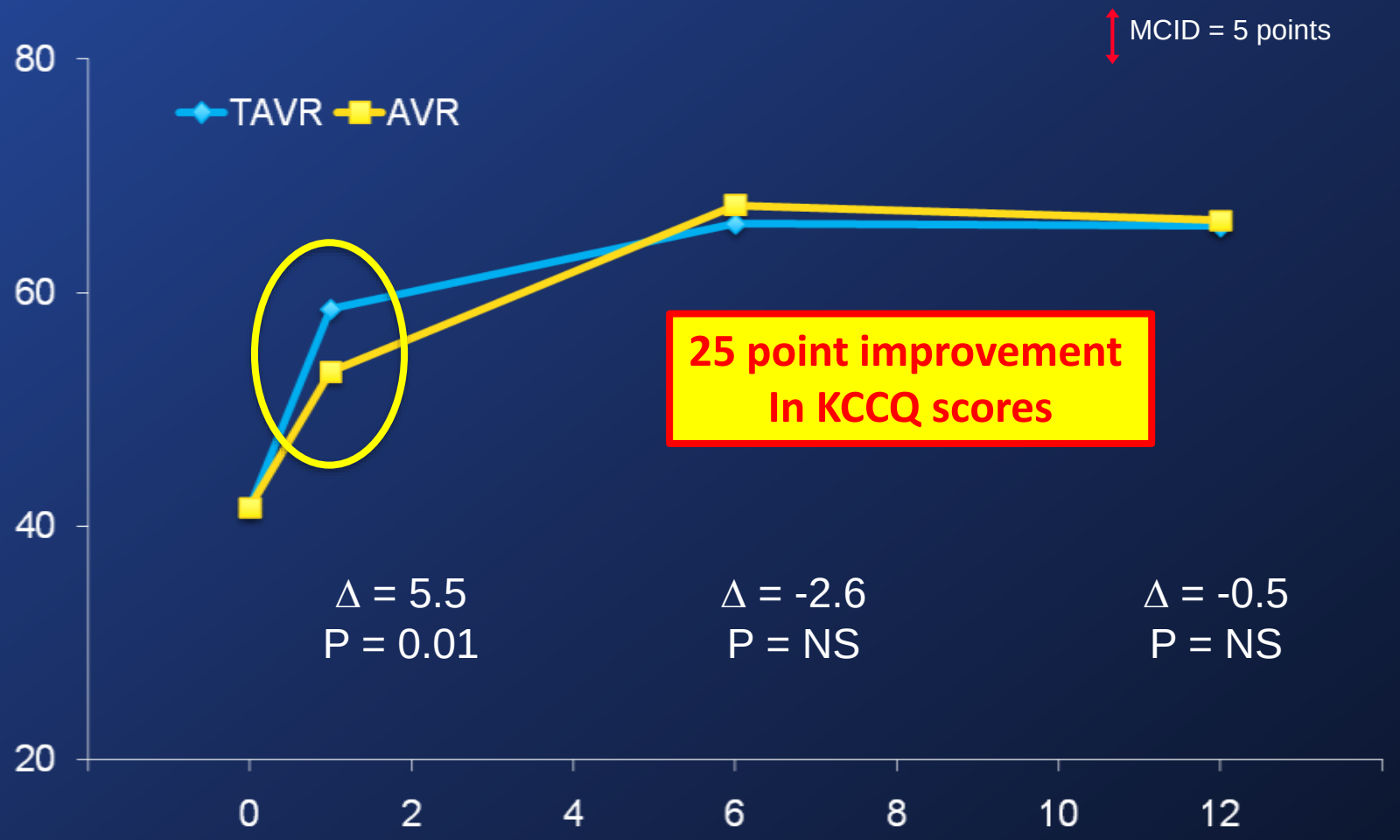
	TAVI	SAVR	P value
Bioprosthetic valve failure			
Valve-related deaths	5.0%	3.7%	0.59
Re-intervention	2.2%	0.7%	0.62
Severe haemodynamic SVD	0.7%	3.0%	0.21

ESC Congress Munich 2018

Sondergaard L. Presented at: Structural Heart Disease Summit 2018, June 2018, Chicago

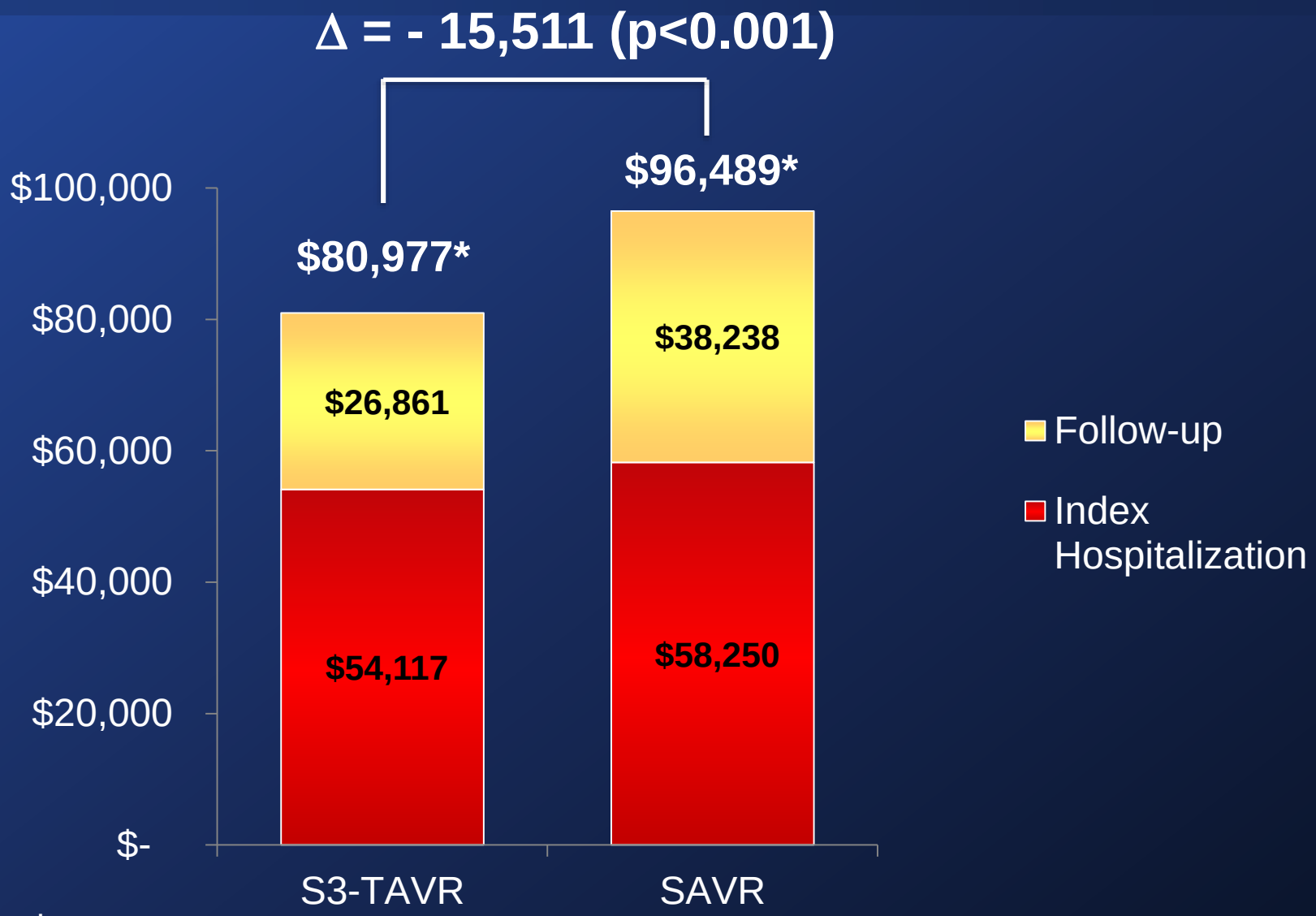
Courtesy: D. Capodanno and L. Sondergaard

Primary Endpoint (PIA RCT)
KCCQ Overall Summary



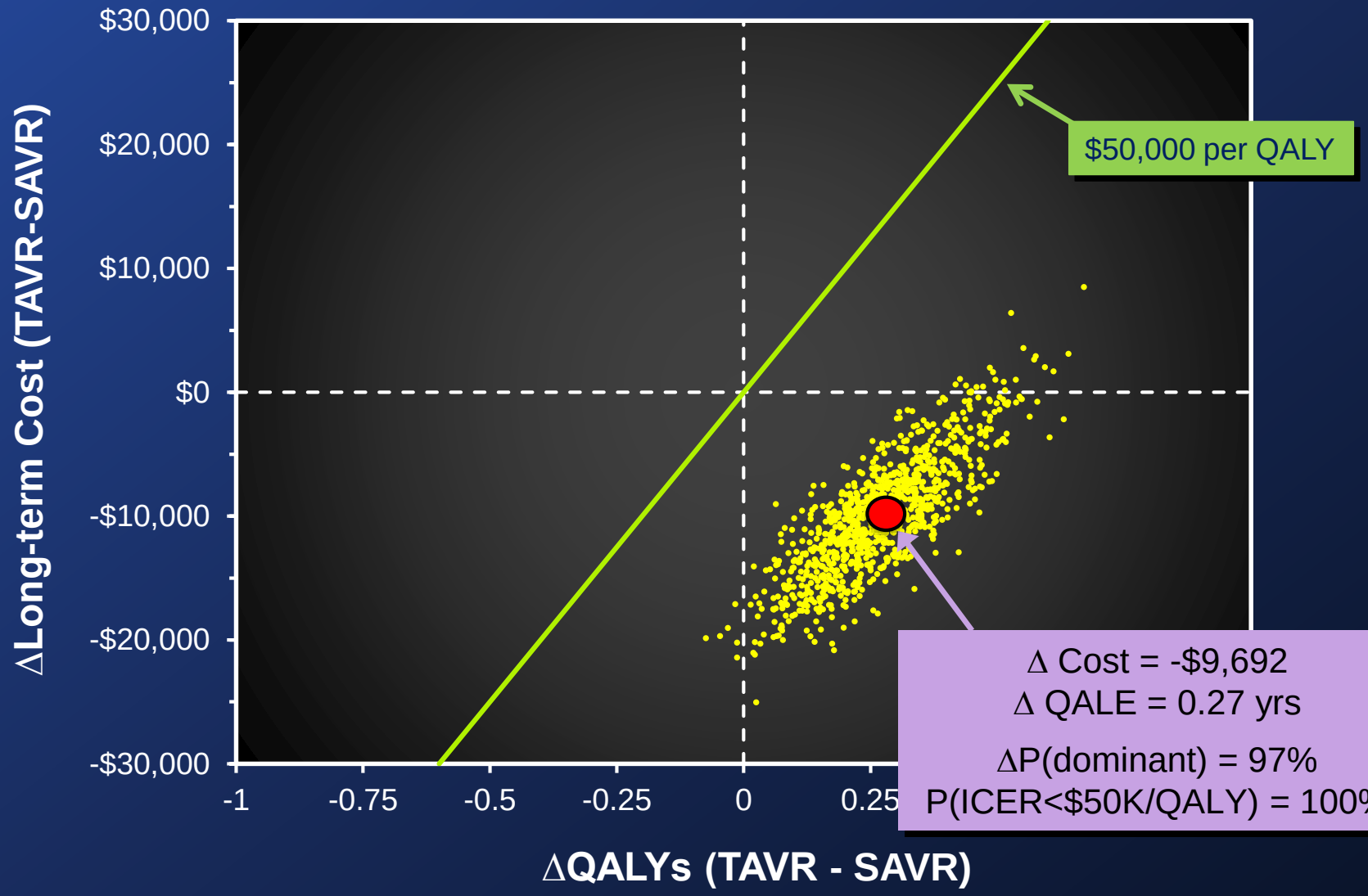
Growth curve analysis; adjusted for baseline
MCID = minimum clinically important difference

Total 1-Year Costs



* Trimmed means

S3-TAVR vs. SAVR: Cost-Effectiveness



* Costs and benefits discounted at 3%

TAVR Landscape - 2018

Where are we NOW?

- **TAVR has become a "routine" procedure in > 1,000 centers worldwide (and almost 600 in the U.S.) for patients with severe symptomatic AS with ≥ moderate surgical risk profiles and appropriate anatomy.**
- **Trans-femoral is the default approach and minimalist strategies are favored.**
- **The heart valve team is the central vehicle for coordinating all Dx and Rx decisions.**

TAVR Landscape - 2018

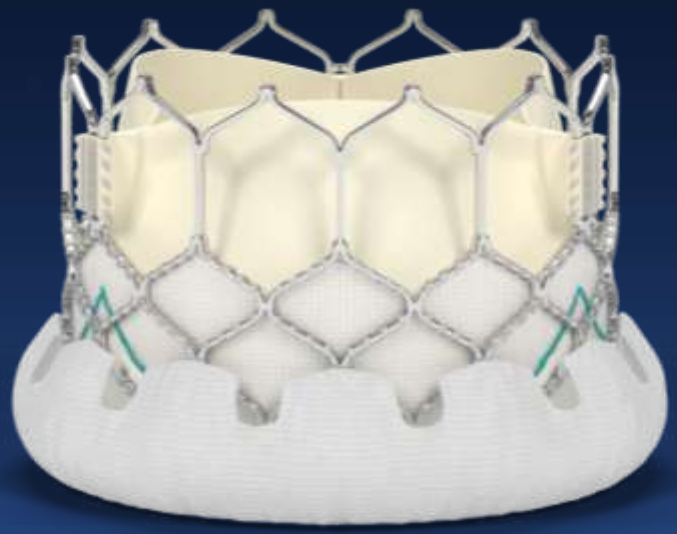
Where are we NOW?

- **Current 'primary' TAVR technology has stabilized but there are new TAVR systems which are being evaluated in the U.S. and elsewhere.**

Current "Standards" for TAVR

MDT Evolut R (PRO)

Edwards Sapien 3



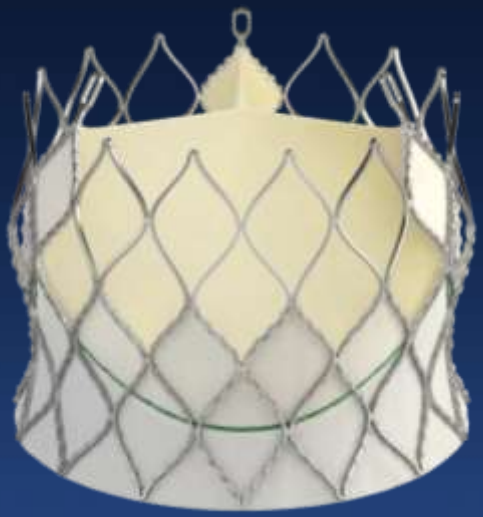
"Next in Line" for TAVR

LOTUS (Edge) **ACURATE neo** **PORTICO**

"Rebooting" and Increasing Momentum

JENA Valve

CENTERA



VENUS A Valve

TAVR Landscape - 2018

Where are we NOW?

- **Current 'primary' TAVR technology has stabilized but there are new TAVR systems which are being evaluated in the U.S. and elsewhere.**
- **New 'accessory' TAVR technology may improve procedural outcomes – most recent, has been the introduction of cerebral embolic protection devices.**

Cerebral Embolic Protection (CEP)

Clinical studies…

JAMA | Original Investigation

Effect of a Cer

JACC VOL. 69, NO. 4, 2017
JANUARY 31, 2017:463-70

Protecti
Cerebra
Transca

Cerebral Embolic Protection During TAVR

A Clinical Event Meta-Analysis

Gennaro Giustino et al

Samir R. Kapadia, M
Robert Zivadinov, M
Saif Anwaruddin, M
Amar Krishnaswam
James M. McCabe,
Maria C. Alu, MS,[b]
Axel Linke, MD,[j,q] on behalf of the SENTINEL Trial Investigators

Compared With Unprotected Procedures

Julia Seeger, MD,[a] Birgid Gonska, MD,[a] Markus Otto, MD,[b] Wolfgang Rottbauer, MD,[a] Jochen Wöhrle, MD[a]

TAVR Accessory Devices

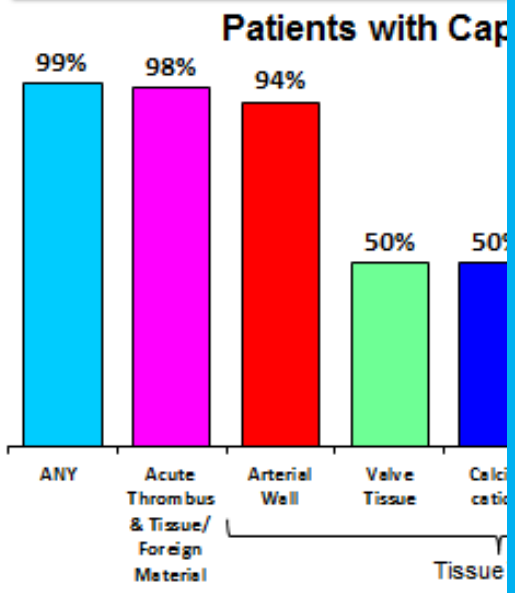
Cerebral Embolic Protection (CEP)

SENTINEL CEP Randomized Trial

Embolic Debris Analysis

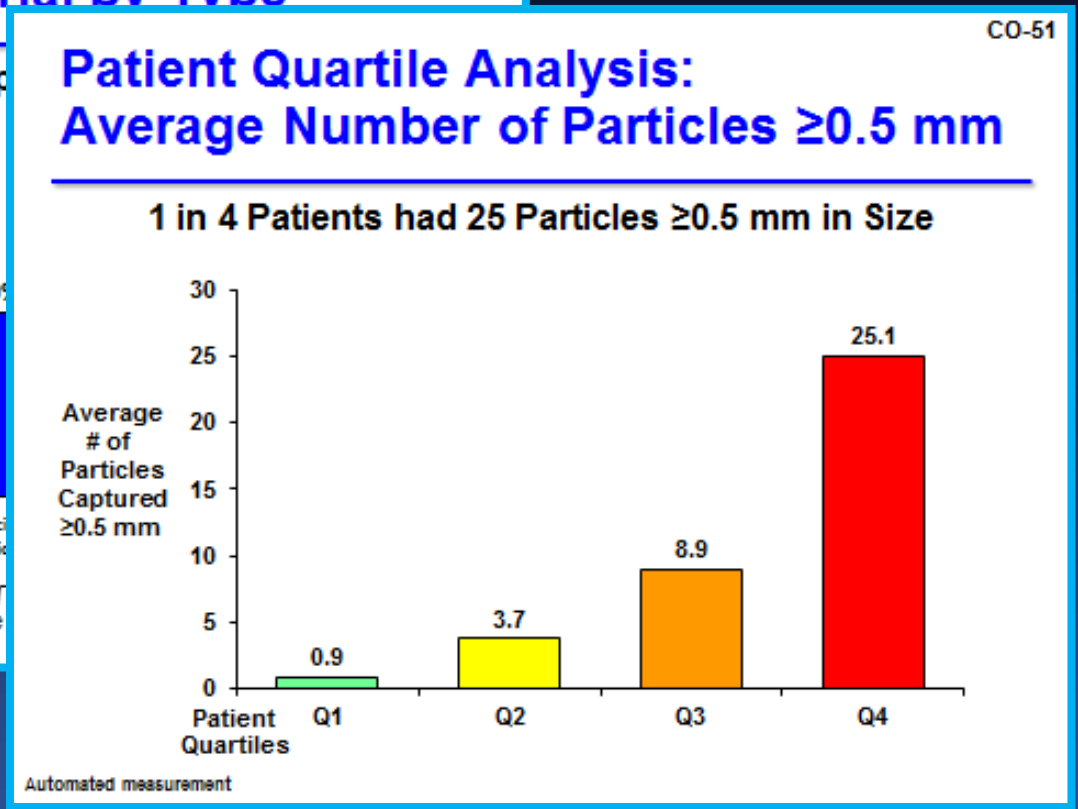
CO-1

SENTINEL Histopathology:
Total Embolic Material by Type



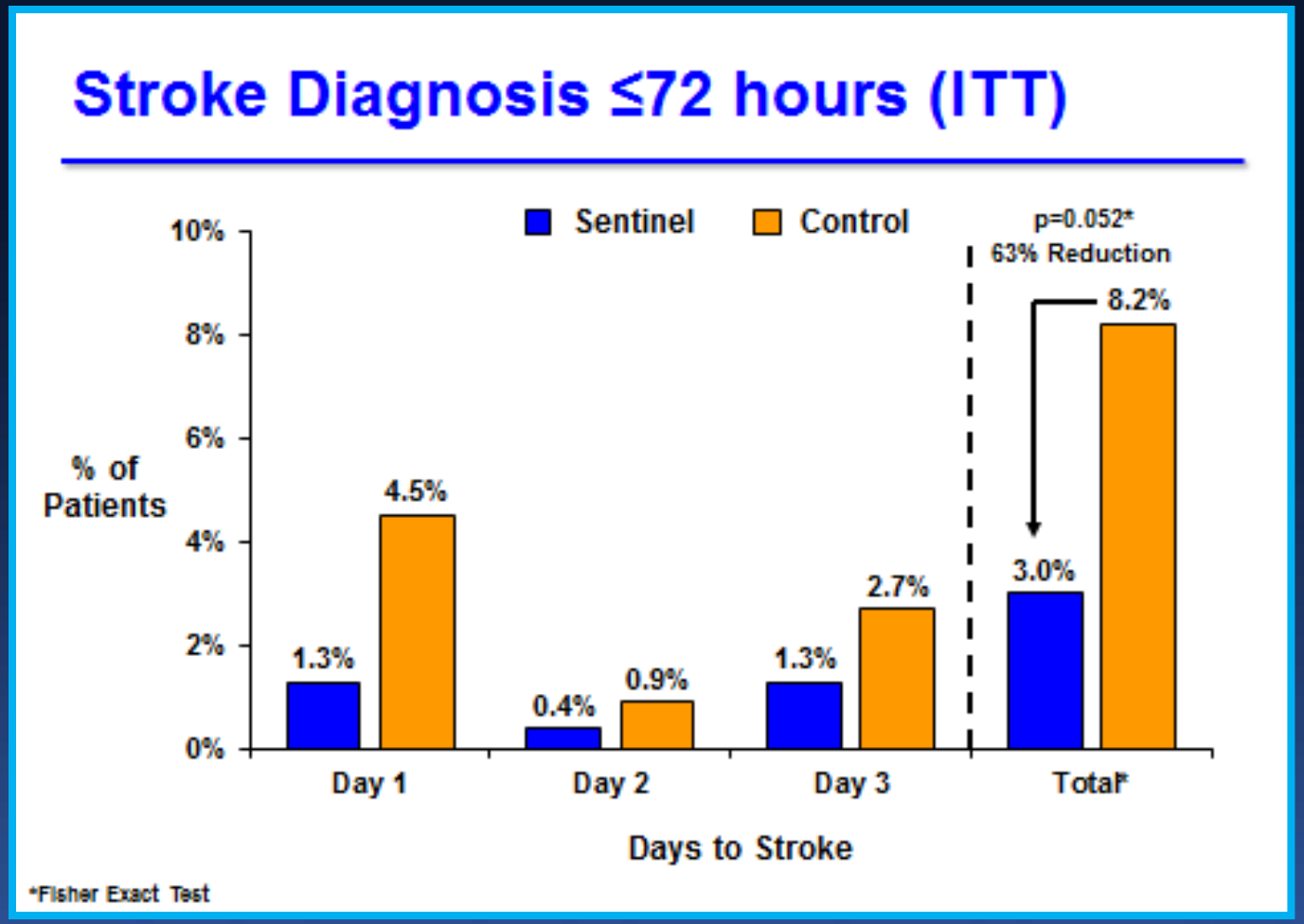
CO-51

Patient Quartile Analysis:
Average Number of Particles ≥0.5 mm



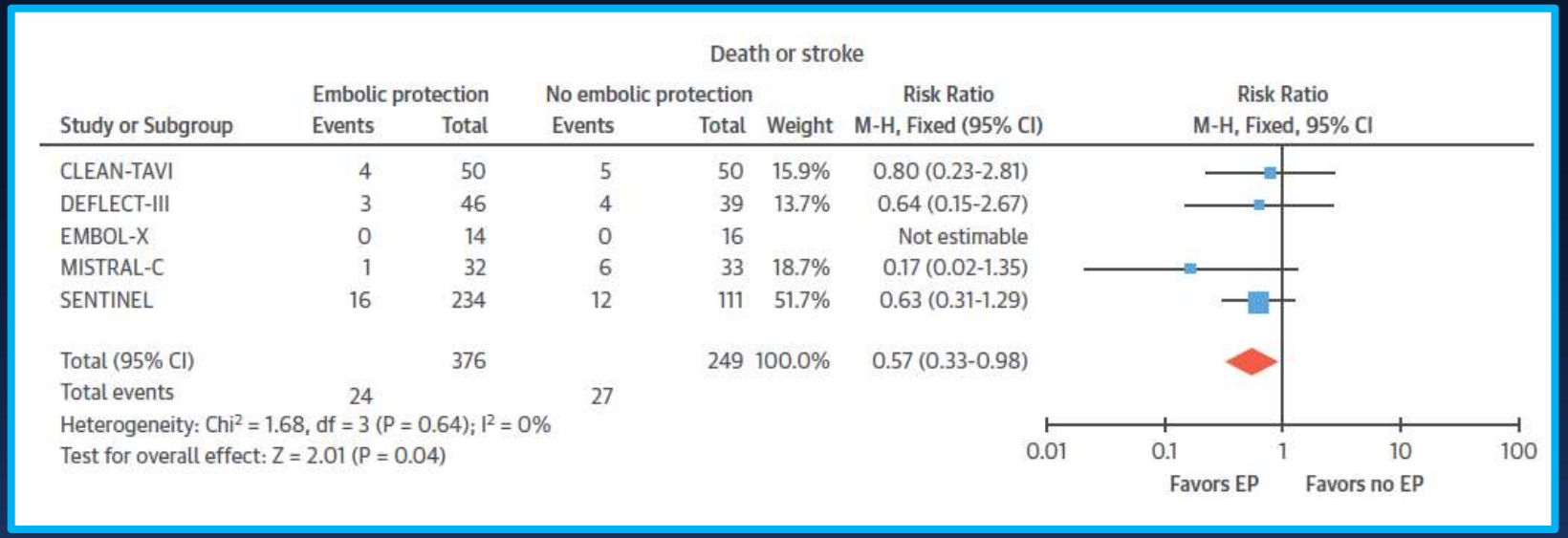
SENTINEL CEP Randomized Trial

Clinical Outcomes



CEP Meta-analysis

Five Studies (n = 625 patients)



Death or stroke

Study or Subgroup	Embolic protection Events	Total	No embolic protection Events	Total	Weight	Risk Ratio M-H, Fixed (95% CI)
CLEAN-TAVI	4	50	5	50	15.9%	0.80 (0.23-2.81)
DEFLECT-III	3	46	4	39	13.7%	0.64 (0.15-2.67)
EMBOL-X	0	14	0	16		Not estimable
MISTRAL-C	1	32	6	33	18.7%	0.17 (0.02-1.35)
SENTINEL	16	234	12	111	51.7%	0.63 (0.31-1.29)
Total (95% CI)		376		249	100.0%	0.57 (0.33-0.98)
Total events	24		27			

Heterogeneity: $Chi^2 = 1.68$, df = 3 (P = 0.64); $I^2 = 0\%$

Test for overall effect: Z = 2.01 (P = 0.04)

Risk Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favors EP Favors no EP

- **Meta-analysis of 5 RCTS of CEP in TAVR (625 pts; 376 with CEP and 249 without CEP)**
- **> 40% reduction in risk of stroke or death (6.4% vs 10.8%; RR: 0.57; 95% CI: 0.33-0.98; p=0.04; I^2 = 0%)**
- ***NNT = 22 to reduce one stroke or death***

Giustino G et al. JACC 2017

Cerebral Embolic Protection (CEP)

SENTINEL ULM Experience

- 802 **all-comer consecutive** TAVR patients at University of Ulm were prospectively enrolled
- A **propensity-score analysis** was done matching the 280 patients protected with Sentinel to 280 control patients

JACC: CARDIOVASCULAR INTERVENTIONS
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http://dx.doi.org/10.1016/j.jcin.2017.06.037

Cerebral Embolic Protection During Transfemoral Aortic Valve Replacement Significantly Reduces Death and Stroke Compared With Unprotected Procedures

Julia Seeger, MD,[a] Birgid Gonska, MD,[a] Markus Otto, MD,[b] Wolfgang Rottbauer, MD,[a] Jochen Wöhrle, MD[a]

- mortality and stroke at 7-days

Wörhle J, Seeger J, et al. DGK Mannheim 2017; CSI-Ulm-TAVR Study clinicaltrials.gov NCT02162069

Sentinel CEP with TAVR

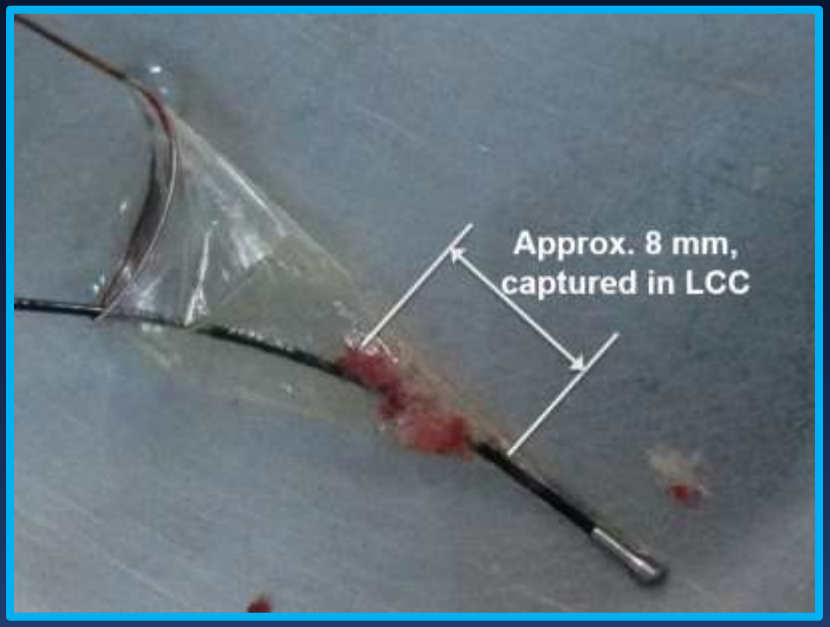
'Real world' registries - stroke reduction

Study Center • Total N • Timing	Unprotected TAVR Patients Neuro Event Rate % (n/N)	Sentinel TAVR Patients Neuro Event Rate % (n/N)	Relative Risk Reduction (RRR)	Number-needed-to-treat (NNT) to avoid one event
Ulm University[1] • N=560 • May 2017	4.6% (13/280)	1.4% (4/280)	70%	22
Pinnacle Health[2] • N=122 • Feb 2018	10% (7/69)	0% (0/53)	100%	10
Erasmus and University Med Centers in Rotterdam and Groningen[3] • N=1047 • June 2018	5.4% (32/589)	1.4% (7/485)	74%	25
	3.6% (21/589)	0.8% (4/485)	78%	36
Cedars Sinai[4] • N=440 • June 2018	4.9% (8/162)	1.1% (3/278)	78%	26

Cerebral Embolic Protection (CEP)

Is it necessary?

Would you take a chance and drive without a seatbelt?



You never know when you"ll need protection!

TAVR Landscape - 2018

What the future will bring…

TAVR Landscape - 2018

Speculations and Predictions

Columbia University Medical Center
NewYork-Presbyterian

TAVR Landscape - 2018

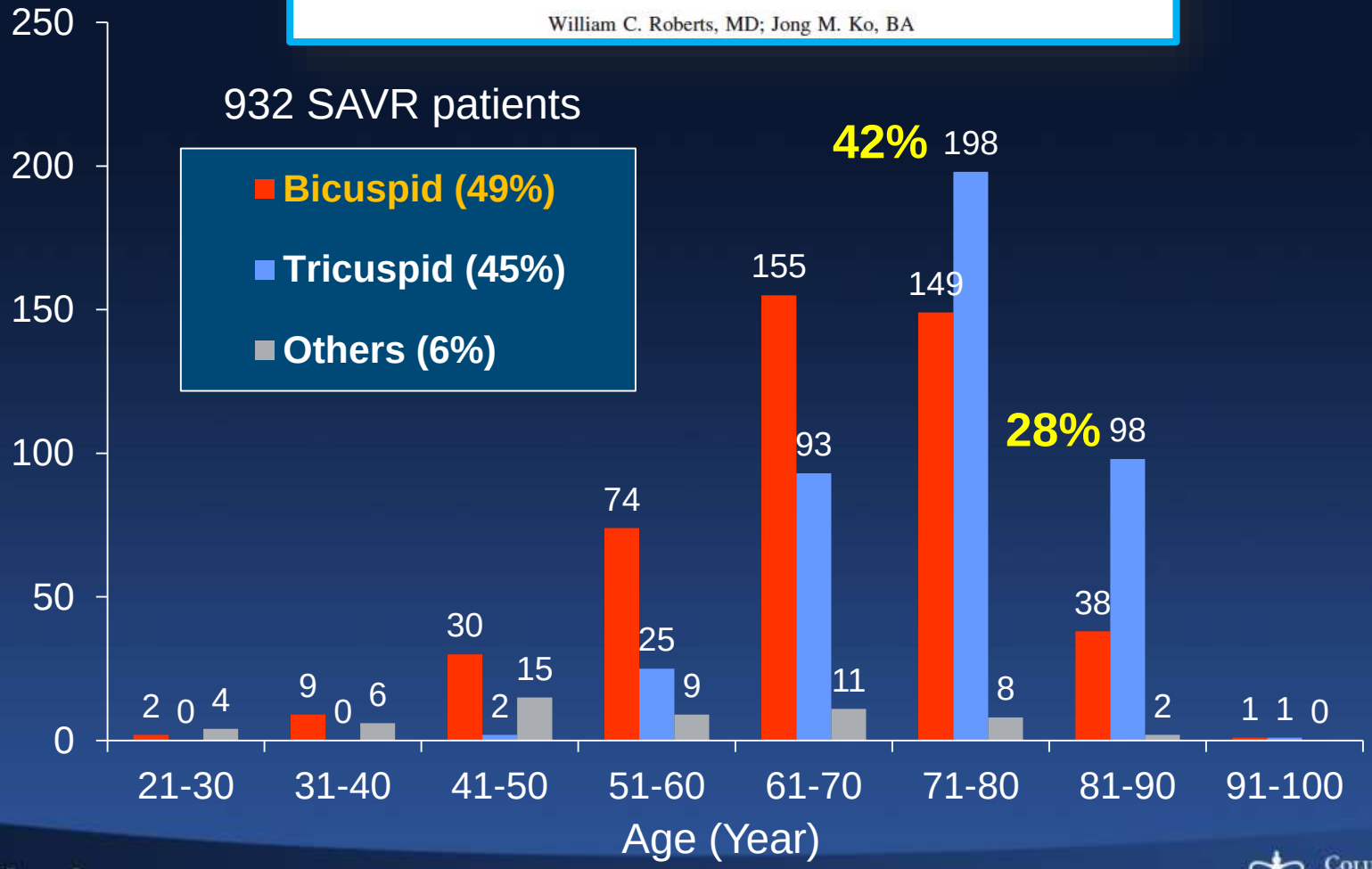
Key Messages

- **The success of TAVR therapy has catalyzed a 'second wave' of clinical studies to explore the expansion of clinical indications (even beyond current surgery).**
  - ✓ Bicuspid AV disease
  - ✓ AS + concomitant disease (CAD, MR, AF)
  - ✓ Severe asymptomatic AS
  - ✓ Moderate AS + CHF
  - ✓ High-risk severe AR

Incidence of BAV in Isolated SAVR

Frequency by Decades of Unicuspid, Bicuspid, and Tricuspid Aortic Valves in Adults Having Isolated Aortic Valve Replacement for Aortic Stenosis, With or Without Associated Aortic Regurgitation

William C. Roberts, MD; Jong M. Ko, BA



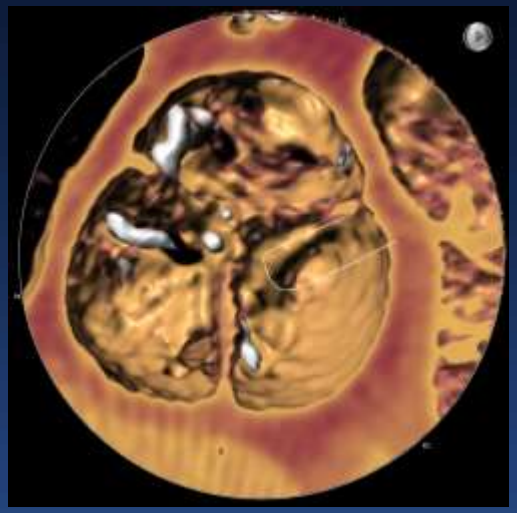
Roberts, WC. Circulation 2005;111:920-925

BAV Classification

CTA System

(from 14 centers in North America, Europe and Asia)

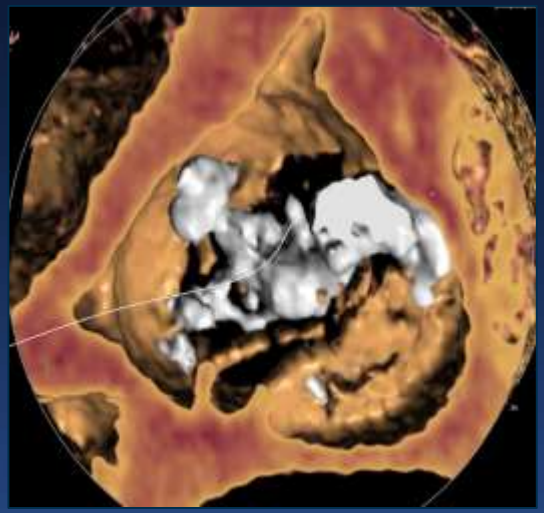
Tricommissural



3 commissures
V-like orifice
"functional or acquired"

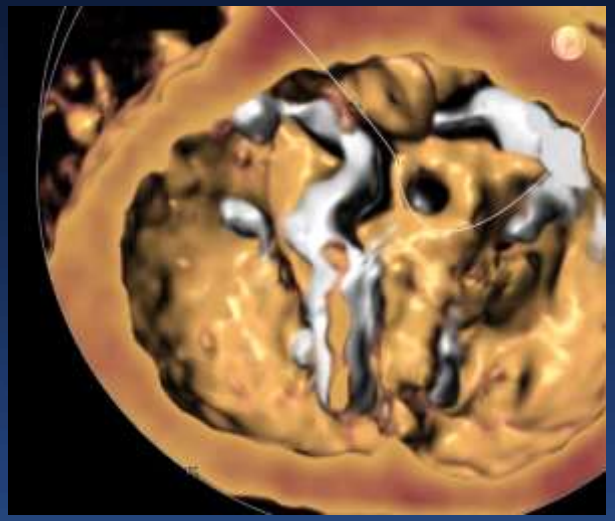
Bicommissural Raphe-type

68%



2 commissures, 1 raphe
Slit-like orifice

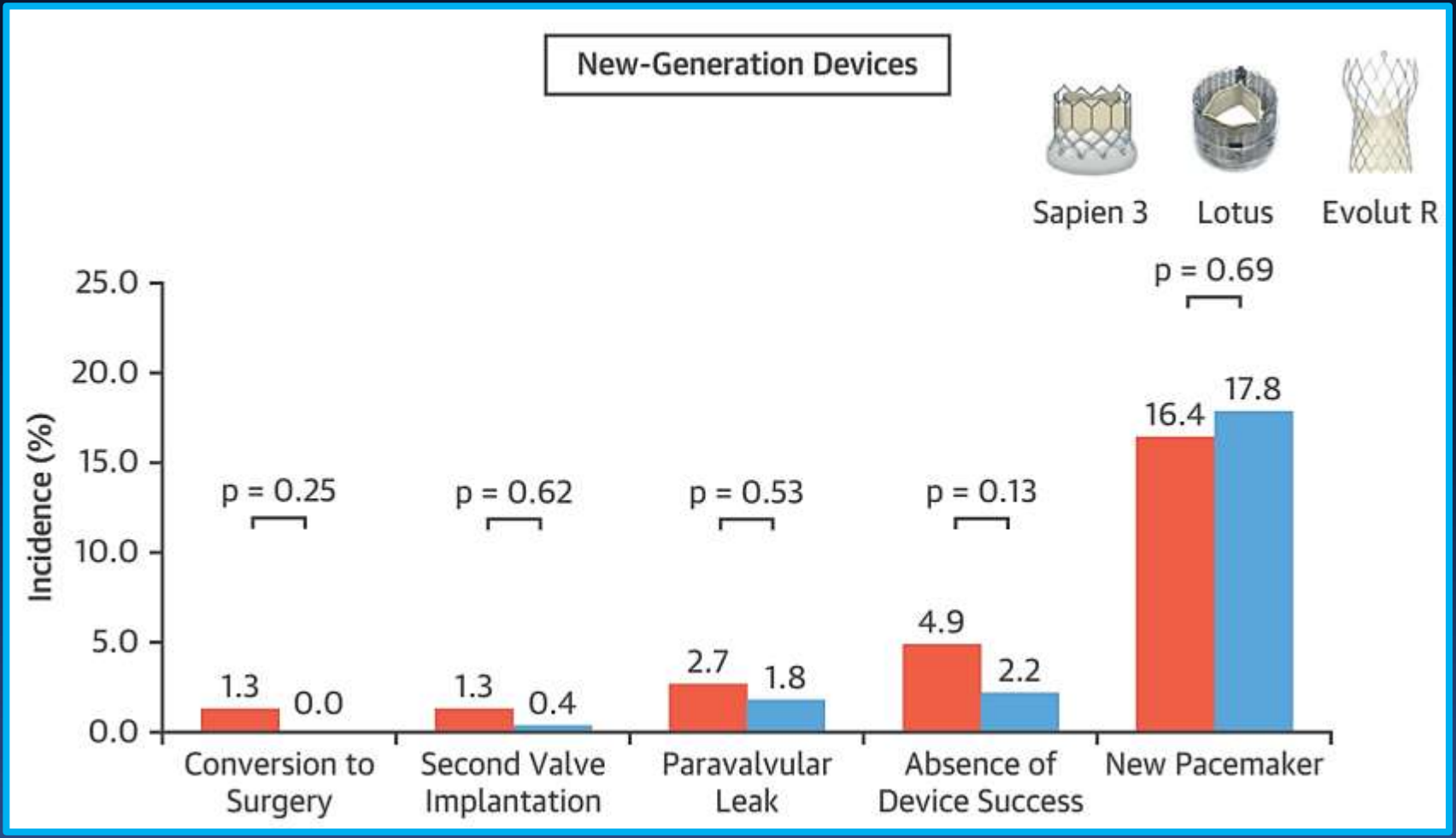
Bicommissural Non Raphe-type



2 commissures, no raphe
Slit-like orifice

Jilaihawi H. JACC Imaging 2016

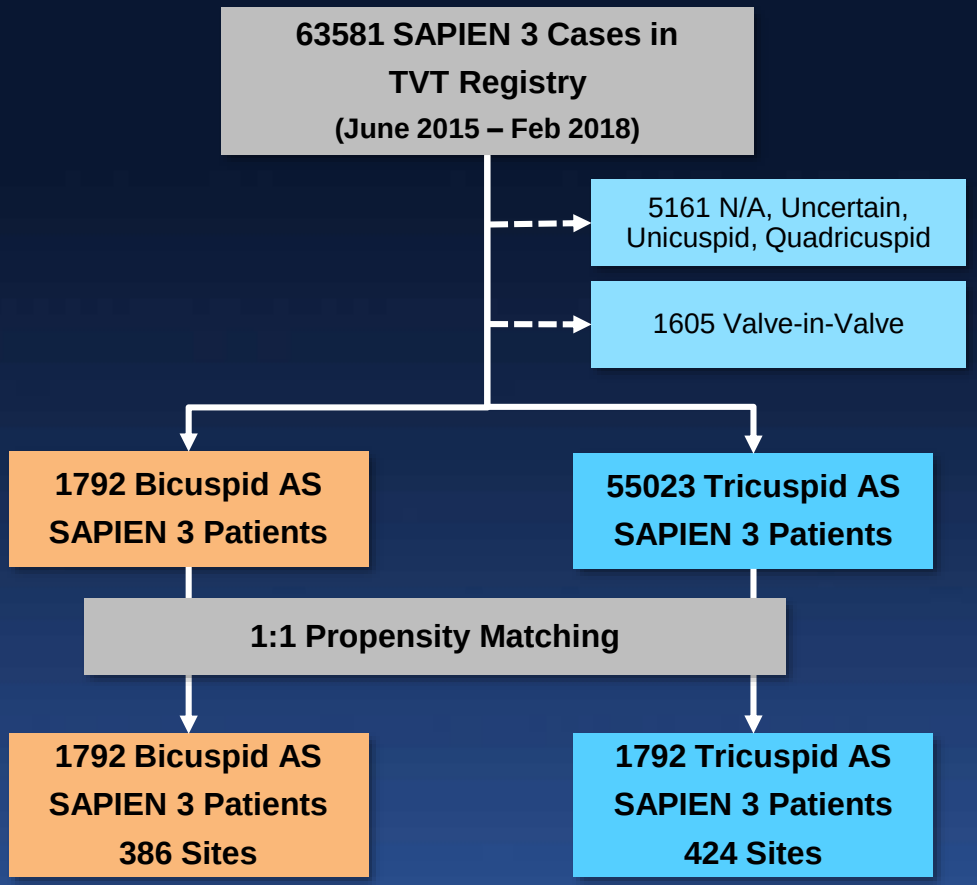
Recent Multicenter BAV – TAVI Registry



Yoon SH et al. JACC 2017;21:2579-89

Bicuspid vs. Tricuspid TAVR Outcomes

A Propensity-Matched Analysis from the TVT Registry



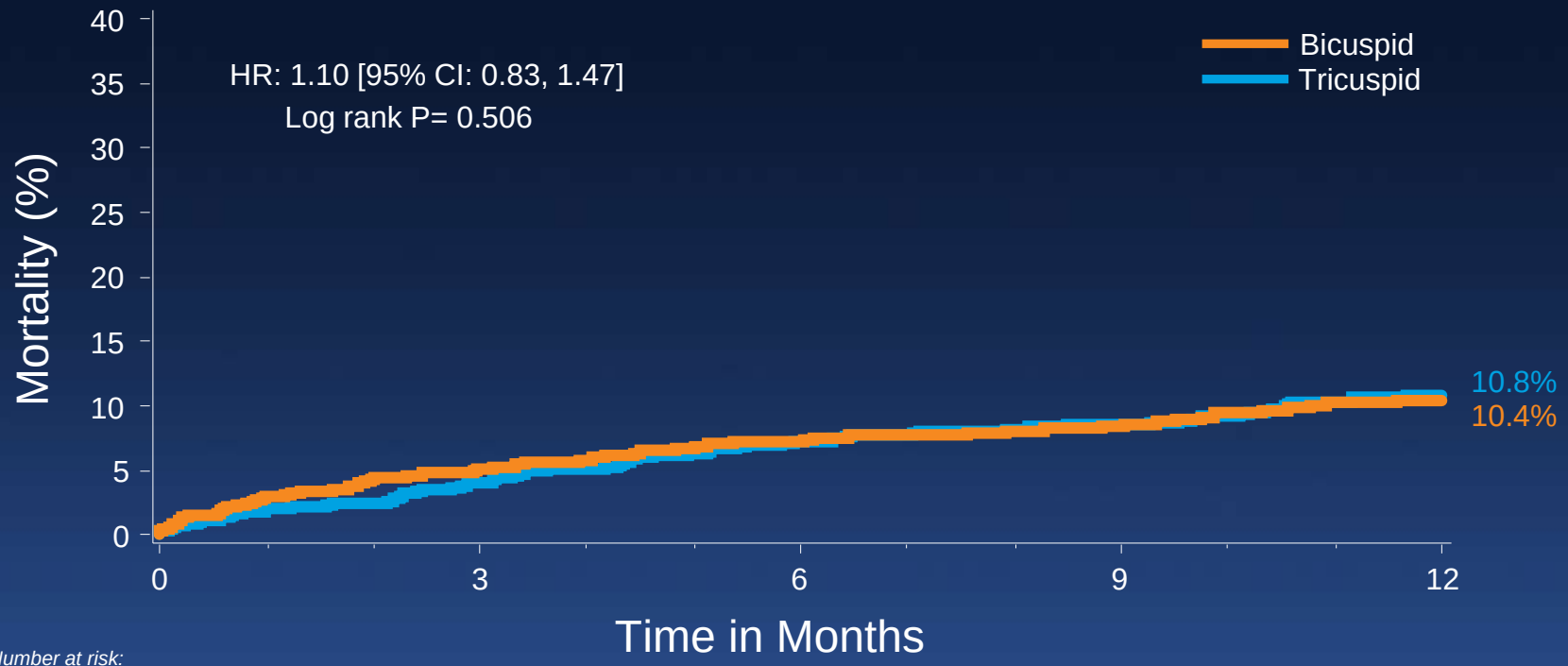
Propensity Matched Analysis

- **1:1 subject selection**
- **24 baseline covariates**
  - Missing values: imputed using Markov Chain Monte Carlo method
- **Logistic regression model**

Bicuspid vs. Tricuspid TAVR Outcomes

A Propensity-Matched Analysis from the TVT Registry

1-Year All-Cause Mortality



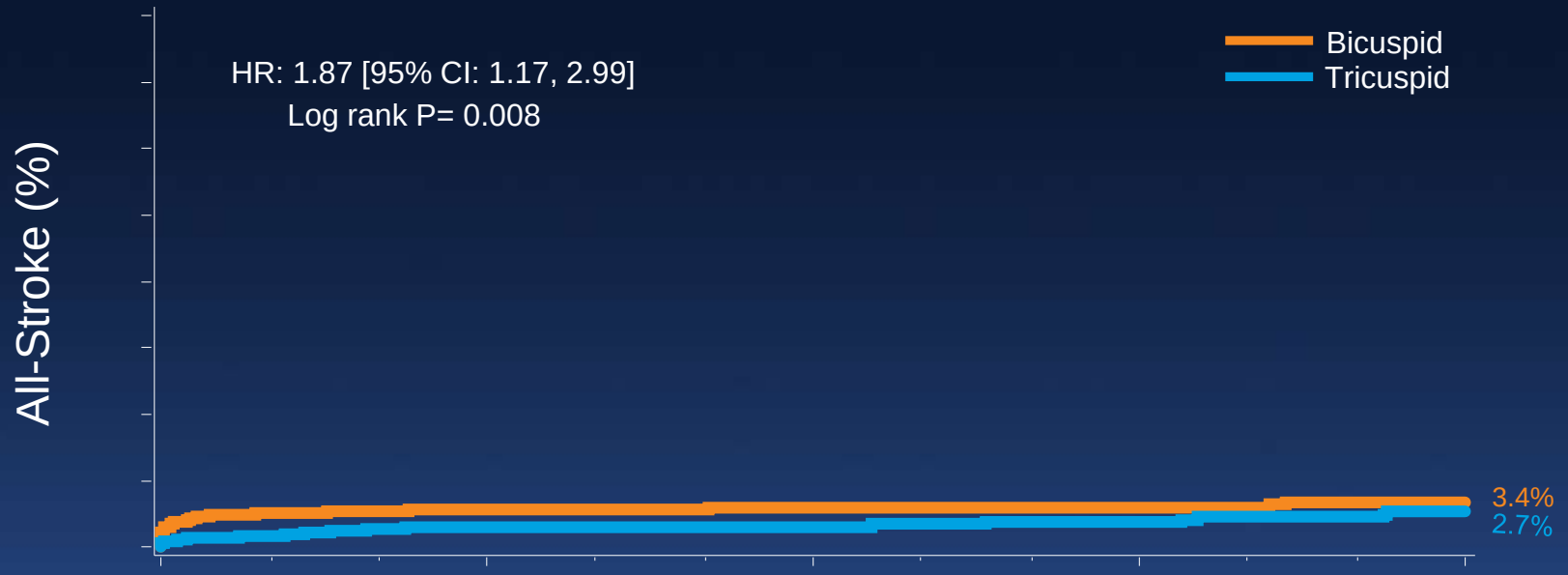
Number at risk:

Bicuspid	1792	552	530	521	372
Tricuspid	1792	626	589	578	417

Bicuspid vs. Tricuspid TAVR Outcomes

A Propensity-Matched Analysis from the TVT Registry

1-Year All Strokes

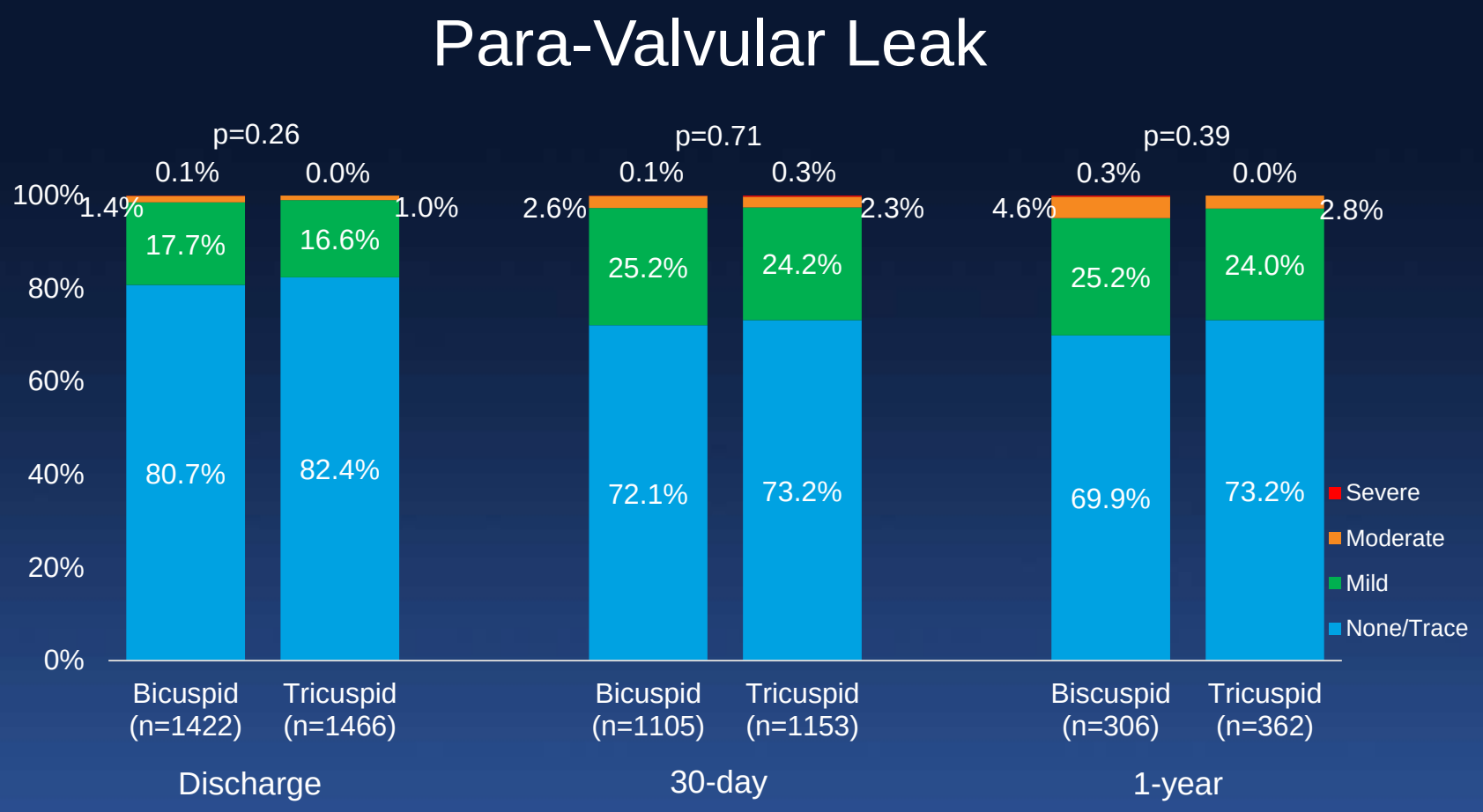


Number at risk:

Bicuspid	1792	546	524	515	366
Tricuspid	1792	615	580	567	407

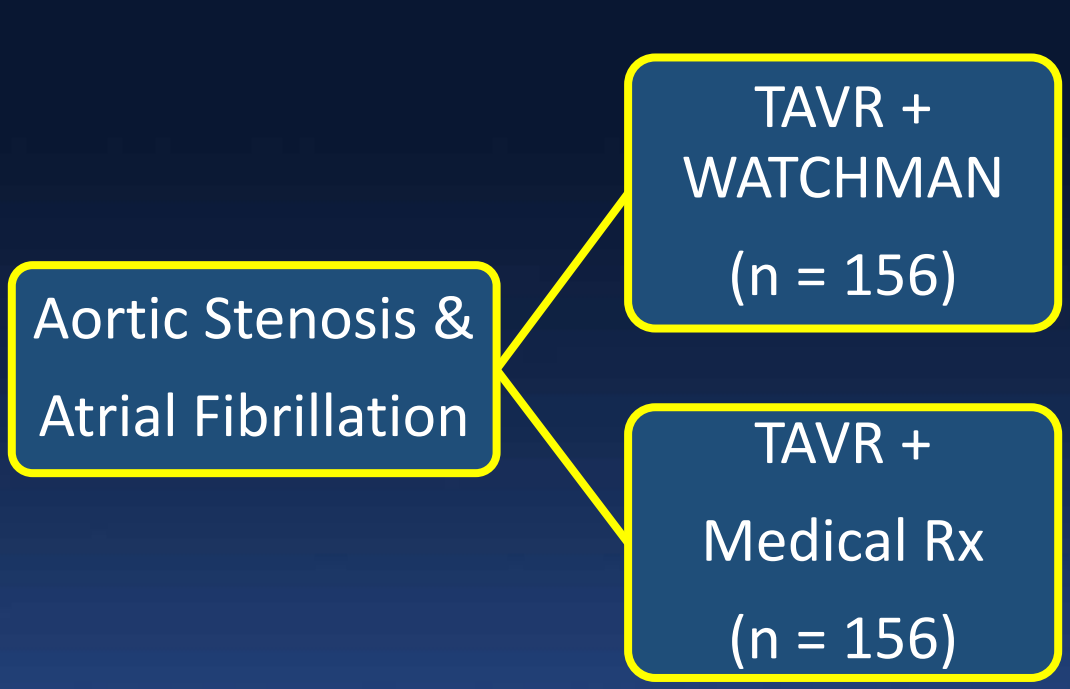
Bicuspid vs. Tricuspid TAVR Outcomes

A Propensity-Matched Analysis from the TVT Registry



AS and Atrial Fibrillation

Watch-TAVR



1º Outcome:

- Death, stroke, bleeding @ 1 year

2º Outcome:

- Components of primary
- Any thromboembolism
- Cardiovascular death
- Re-hospitalization
- QoL (KCCQ-12)
- Procedural costs

National PIs: Samir Kapadia & Martin Leon

Grant support: Boston Scientific

EARLY TAVR Trial
Study Flow

THE PARTNER 3 TRIAL

Asymptomatic Severe AS and 2D-TTE (PV ≥4m/s or AVA ≤1 cm^2)
Exclusion if patient is symptomatic, age <65 yo, EF<50%, concomitant surgical indications, or STS >8

Treadmill Stress-Test

Stress-Test Normal

CTA and Angiography
TF- TAVR eligibility

Early-TAVR Randomized Trial

Randomization 1:1
Stratified by STS (<3 vs ≥3)

TF- TAVR

Clinical Surveillance

Stress-Test Abnormal

Early TAVR Registry

1109 pts, 75 US sites

Primary Endpoint (superiority): 2-year composite of all-cause mortality, all strokes, and repeat hospitalizations (CV)

Principal Investigators:
Philippe Généreux, Allan Schwartz
Chair: Martin B. Leon

TAVR UNLOAD Trial

Study Design

(600 patients, 1:1 Randomized)

PIs: Nicolas M. Van Mieghem and Martin B. Leon

TAVR UNLOAD Trial

International Multicenter Randomized

Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS

R

TAVR + OHFT

OHFT Alone

Follow-up:
1 month
6 months
1 year

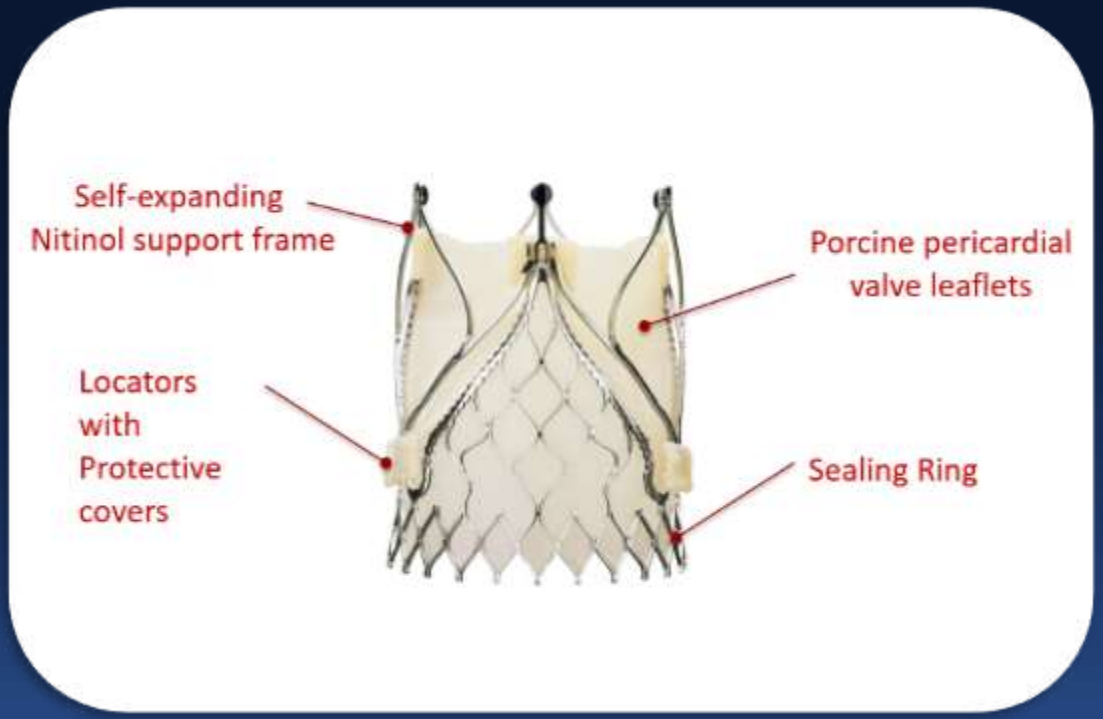
Clinical endpoints
Symptoms
Echo
QoL

Primary Endpoint
Hierarchical occurrence of:
- **All-cause death**
- **Disabling stroke**
- **Hospitalizations for HF, aortic valve disease**
- **Change in KCCQ**

Reduced AFTERLOAD
Improved LV systolic and diastolic function

Jena Valve TAVR System

Ongoing EFS for AS and AR



Valve sizes: 23, 25, and 27 mm

Features

- self-expanding nitinol frame
- bovine pericardial leaflets
- supra-annular valve position
- clipping of native leaflets
- mitigated risk of coronary obstruction, new PPM, and annulus rupture due to pre-defined position in the annulus

TAVR Landscape - 2018

Key Messages

- **The success of TAVR therapy has catalyzed a 'second wave' of clinical studies to explore the expansion of clinical indications (even beyond current surgery).**
- **There are many innovative TAVR-related technologies which are being actively explored!**

Tissue Engineered Heart Valves

the promise…

Non living

Mechanical valves

Bioprosthetic valves

Living

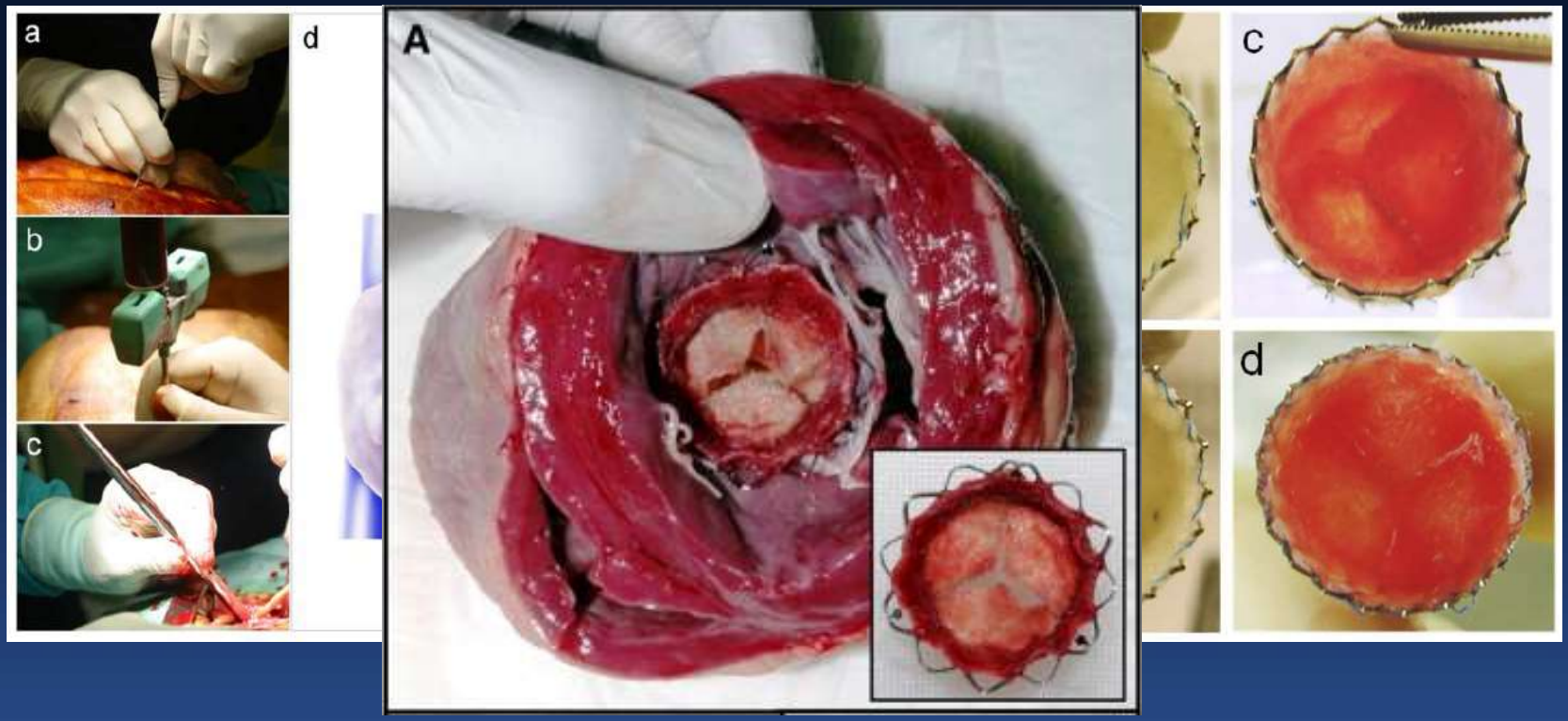
1960

2020

One valve for life!

Zurich Tissue Engineered Heart Valve

A "Living" Aortic Valve



Courtesy of Simon P. Hoerstrup, MD, PhD

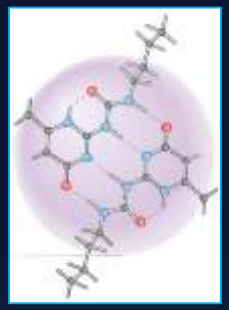
Endogenous tissue restoration

combining 3 scientific disciplines

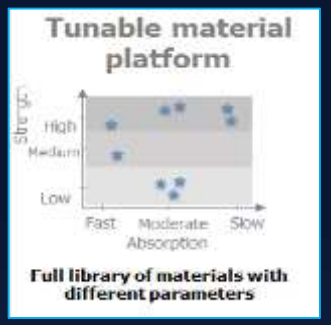
Supramolecular Chemistry

Jean Marie Lehn

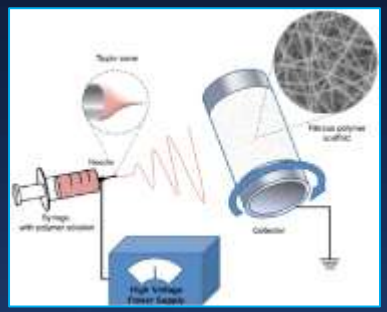
Nobel prize for Supramolecular Chemistry , 1987

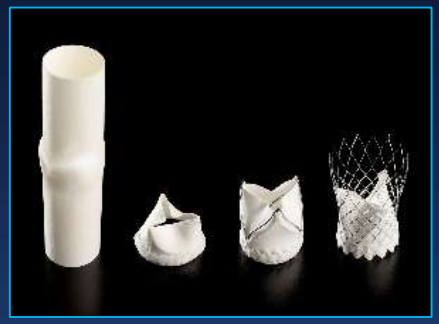


Sijbesma, Science, 1997

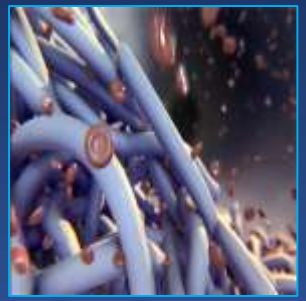


Electrospinning



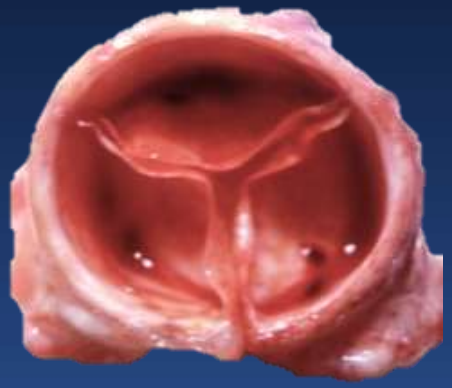


Regenerative Medicine



Xeltis

Endogenous Tissue Restoration (ETR)

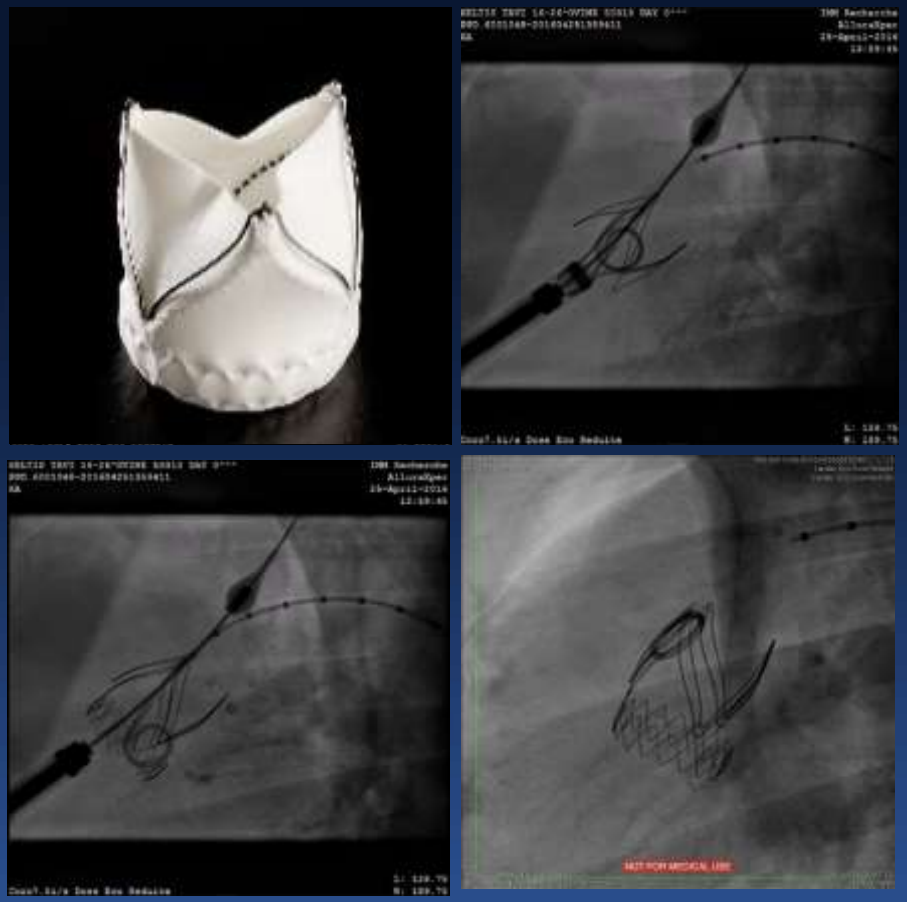


Valve after bioabsorption

- Synthetic matrix made of novel bioabsorbable supramolecular polymers using electrospinning techniques
- Polymer leaflets mounted on nitinol self-expanding frame
- Regrowth of endogenous tissue coincident with bioabsorption of polymer implant
- Natural self-healing anti-inflammatory leaflets

Xeltis

Endogenous Tissue Restoration (ETR)



Aortic Valve

- Safety demonstrated in >50 sheep
- 96% device success
- 3 and 6 months FU complete
- Preliminary 12 months data available and encouraging
- Hemodynamic performance stable over time

Novel AS Imaging Technology

Bay Labs – Echo acquisition

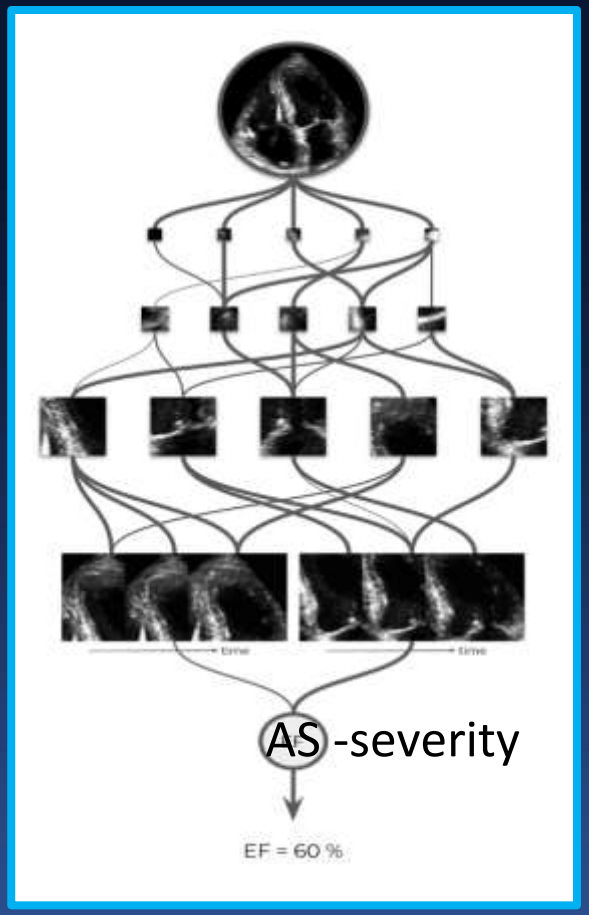
Available hand-held POCUS devices

Prompts for BL echo acquisition

JAMA Cardiology 2018

Novel AS Imaging Technology

Bay Labs – Echo interpretation



Training: > 25,000 complete AS echo studies

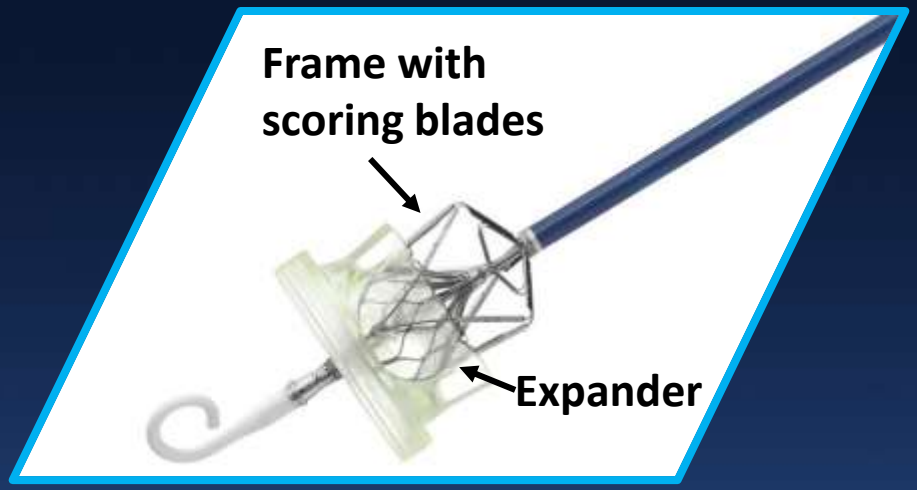
Input: PLAX and PSAX shown to the pre-trained network

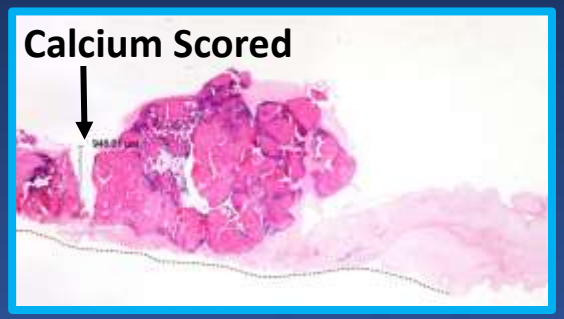
Output: network integrates responses and makes diagnosis of valvular heart disease, rheumatic vs. non-rheumatic, and estimates the severity of AS (when present)

TAVR Accessory Devices

Aortic Valve Remodeling (1)

Leaflex AVRT



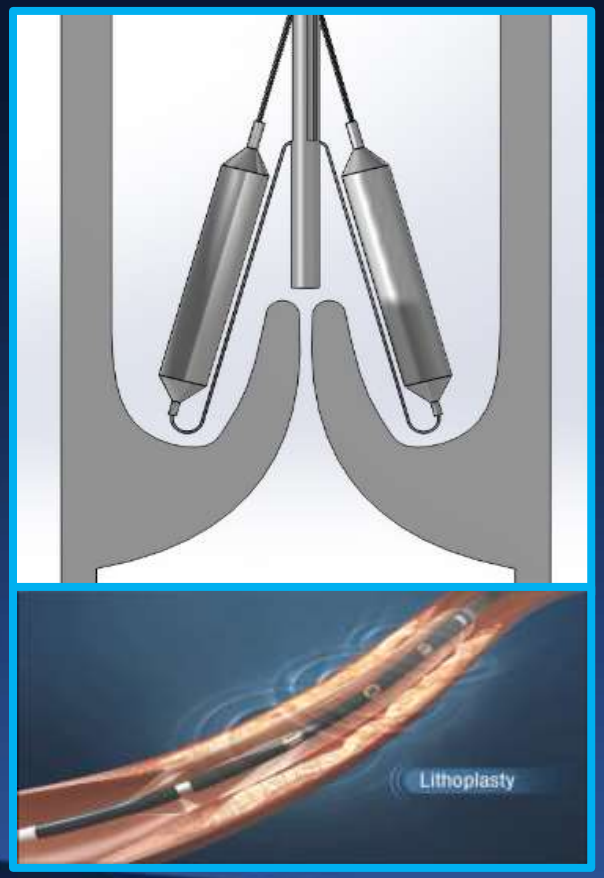


- Mechanical scoring blades fracture leaflet calcium and improve leaflet mobility
- 13 Fr catheter
- Non-occlusive (no PM)
- Can be used as (1) stand-alone, (2) bridge to TAVR/SAVR or (3) preparation for TAVR (heavily calcified valves)

TAVR Accessory Devices

Aortic Valve Remodeling (2)

Lithoplasty for Aortic Leaflet Restoration



- *Electro-hydraulic lithotripsy in a balloon*; microsecond bubble expansion and collapse travels thru balloon and disrupts calcium
- Supra-vavular approach
- Procedural hemodynamic stability; no need for PM
- Trans-femoral access
- Preparation for TAVR preparation or stand-alone therapy

TAVR Landscape - 2018

Key Messages

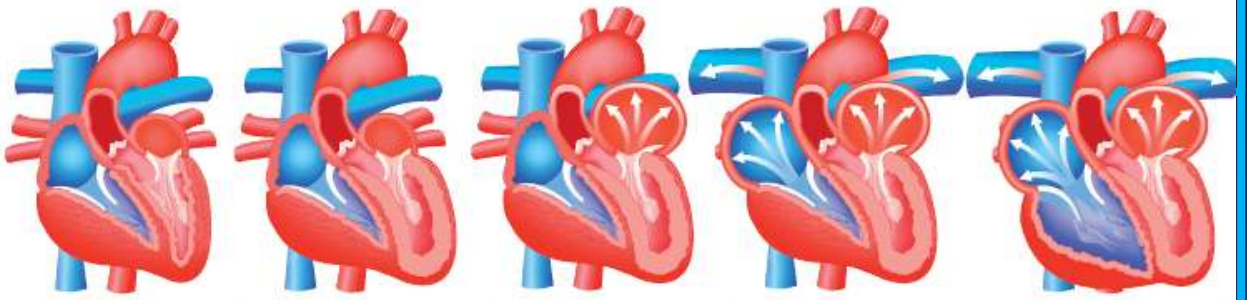
- **The success of TAVR therapy has catalyzed a 'second wave' of clinical studies to explore the expansion of clinical indications (even beyond current surgery).**
- **There are many innovative TAVR-related technologies which are being actively explored!**
- **In the future, AS classification schemes and therapy trigger points will be redefined**

European Heart Journal (2017) **00**, 1–9
doi:10.1093/eurheartj/ehx381

FASTTRACK CLINICAL RESEARCH

Staging classification of aortic stenosis based on the extent of cardiac damage

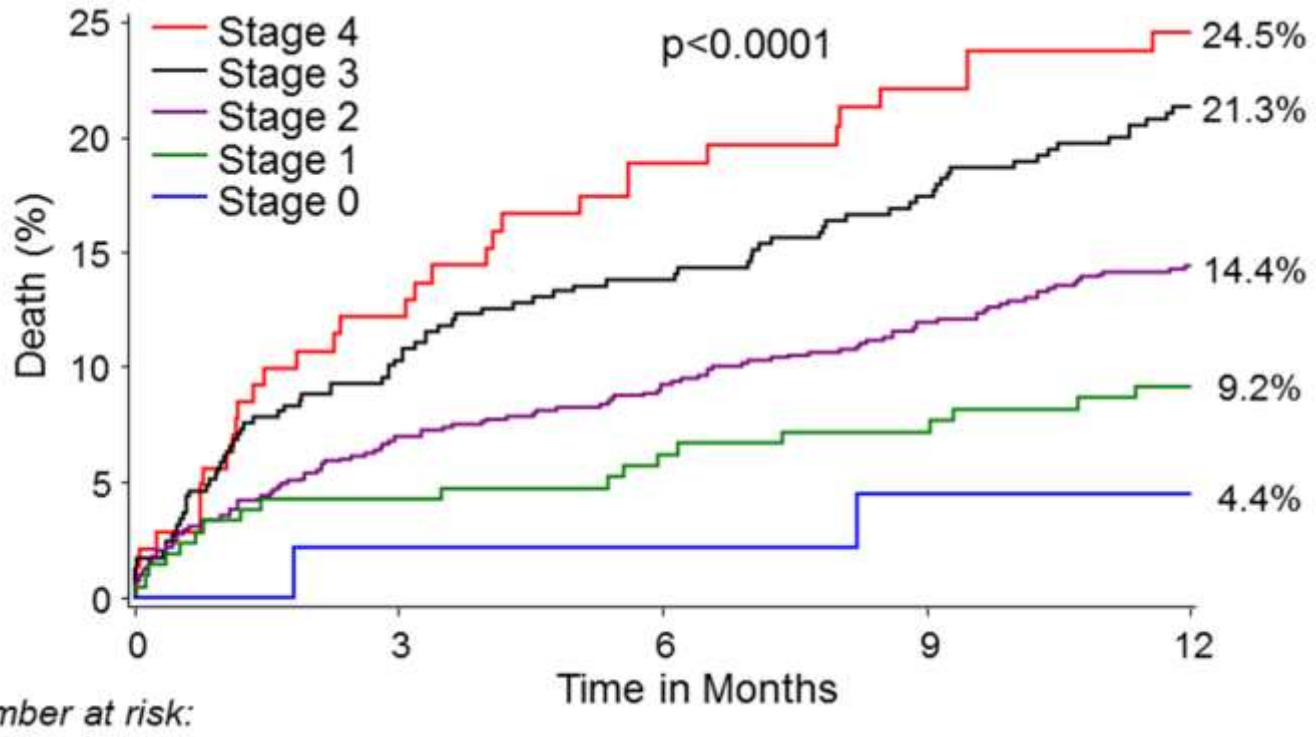
Philippe Généreux[1,2,3], Philippe Pibarot[4], Björn Redfors[1,5], Michael J. Mack[6], Raj R. Makkar[7], Wael A. Jaber[8], Lars G. Svensson[8], Samir Kapadia[8], E. Murat Tuzcu[8], Vinod H. Thourani[9], Vasilis Babaliaros[9], Howard C. Herrmann[10], Wilson Y. Szeto[10], David J. Cohen[11], Brian R. Lindman[12], Thomas McAndrew[1], Maria C. Alu[13],



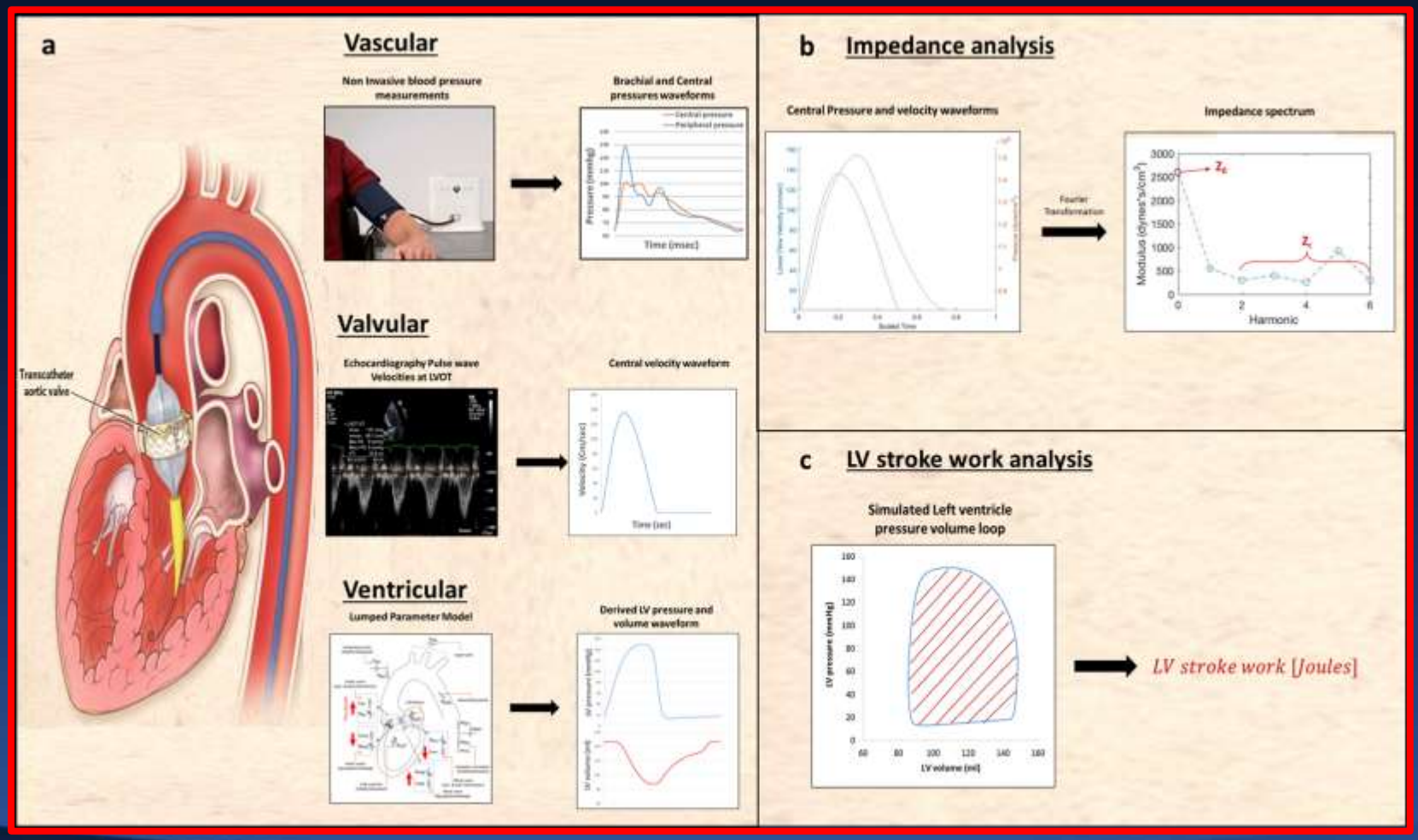
Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m² (Male) >95 g/m² (Female)	Indexed left atrial volume >34mL/m²	Systolic Pulmonary hypertension ≥60 mmhg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

European Heart Journal (2017) **00**, 1–9
doi:10.1093/eurheartj/ehx381

Staging classification of aortic stenosis based on the extent of cardiac damage



New Hypothesis: Ventricular, Valvular and Vascular Dynamics Drive Aortic Stenosis (and should influence treatment decisions)



Courtesy of E. Edelman and colleagues

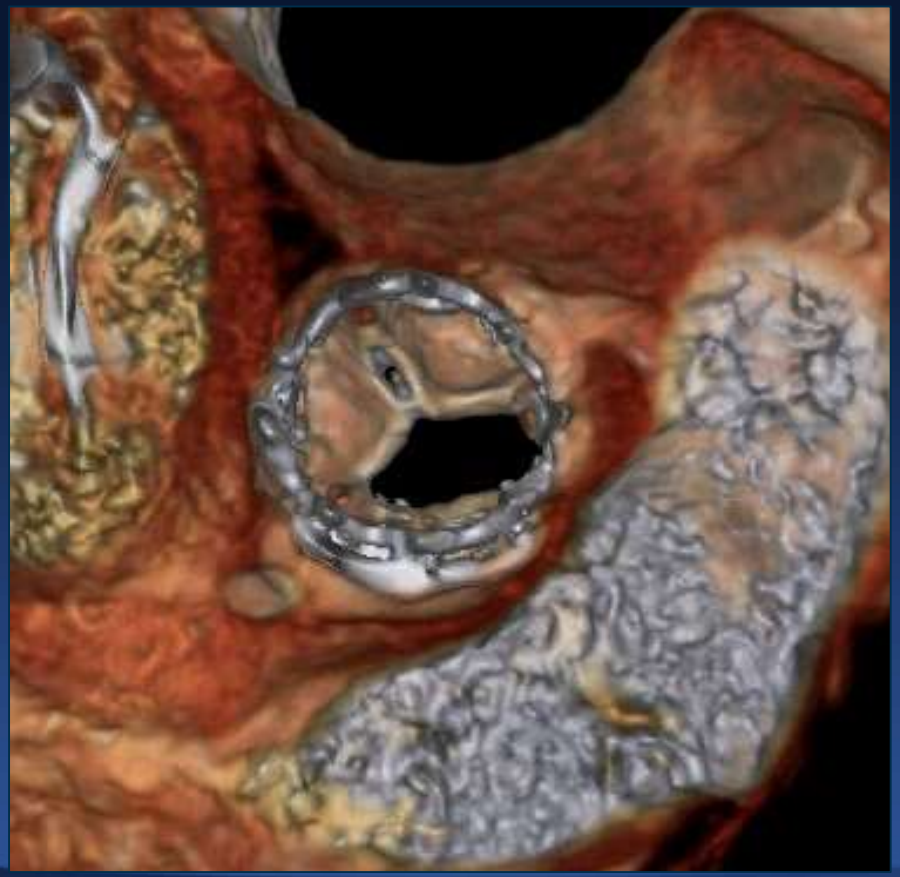
TAVR Landscape - 2018

Key Messages

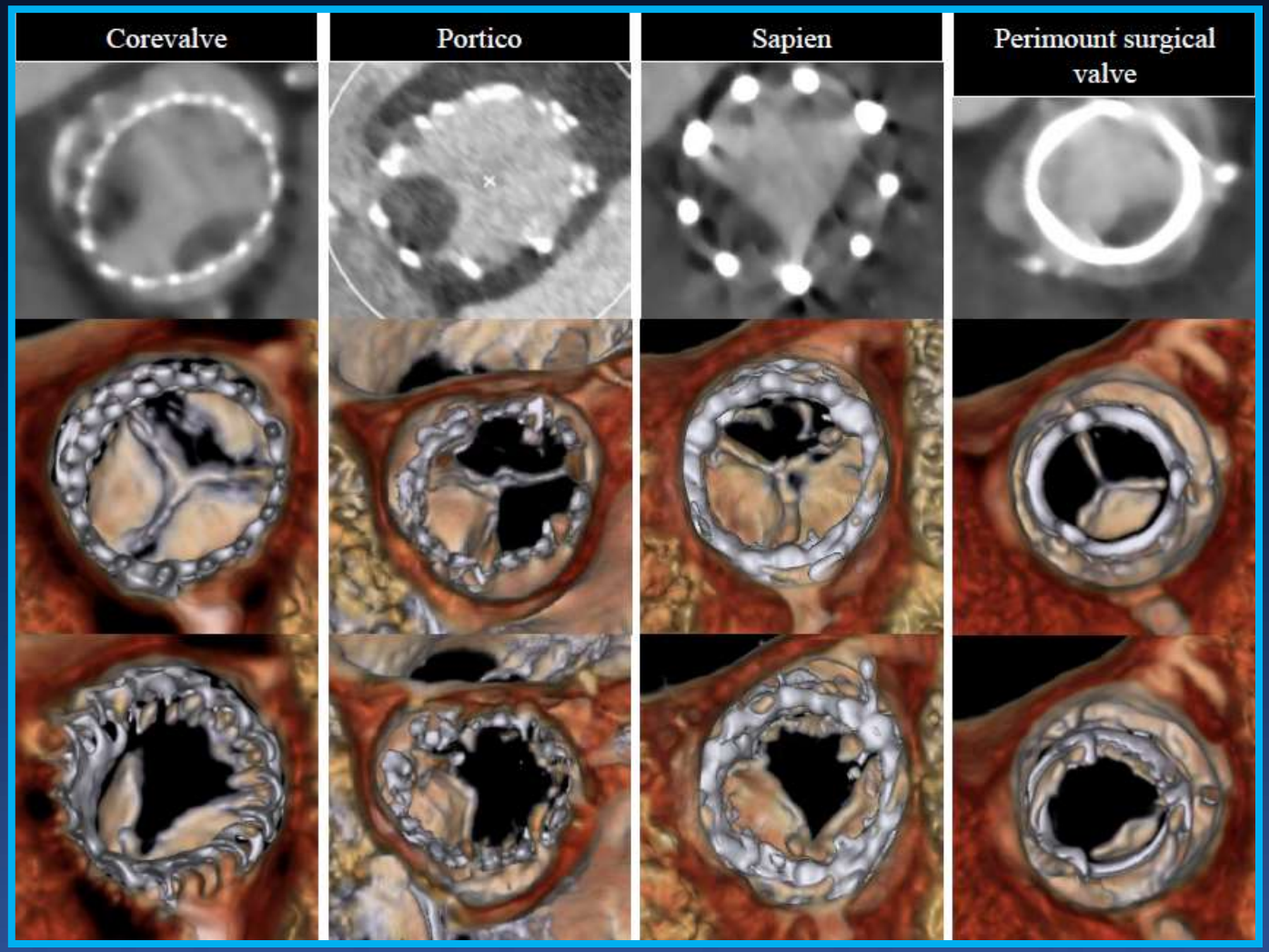
- **There are also many 'gaps' in TAVR knowledge which must be addressed (e.g. valve leaflet abnormalities, late TAVR SVD/durability, coronary access considerations, and optimal adjunctive pharmacotherapy).**

Valve Leaflet Abnormalities

Severely reduced leaflet motion noted in 2 patients in the early part of the U.S. Portico IDE study

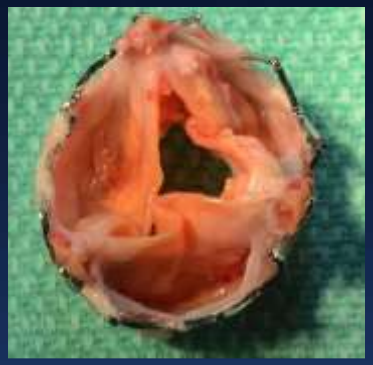


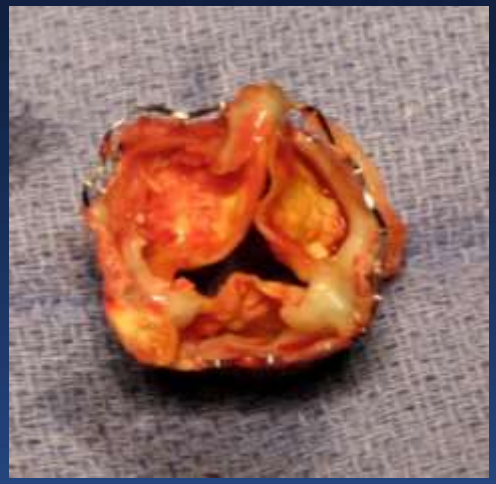
Valve Leaflet Abnormalities



Makkar, et al. NEJM 2015

All TAVR systems will certainly demonstrate evidence of valve degeneration during long-term (> 5 years) assessments, especially if echo criteria are applied in the definitions of durability!



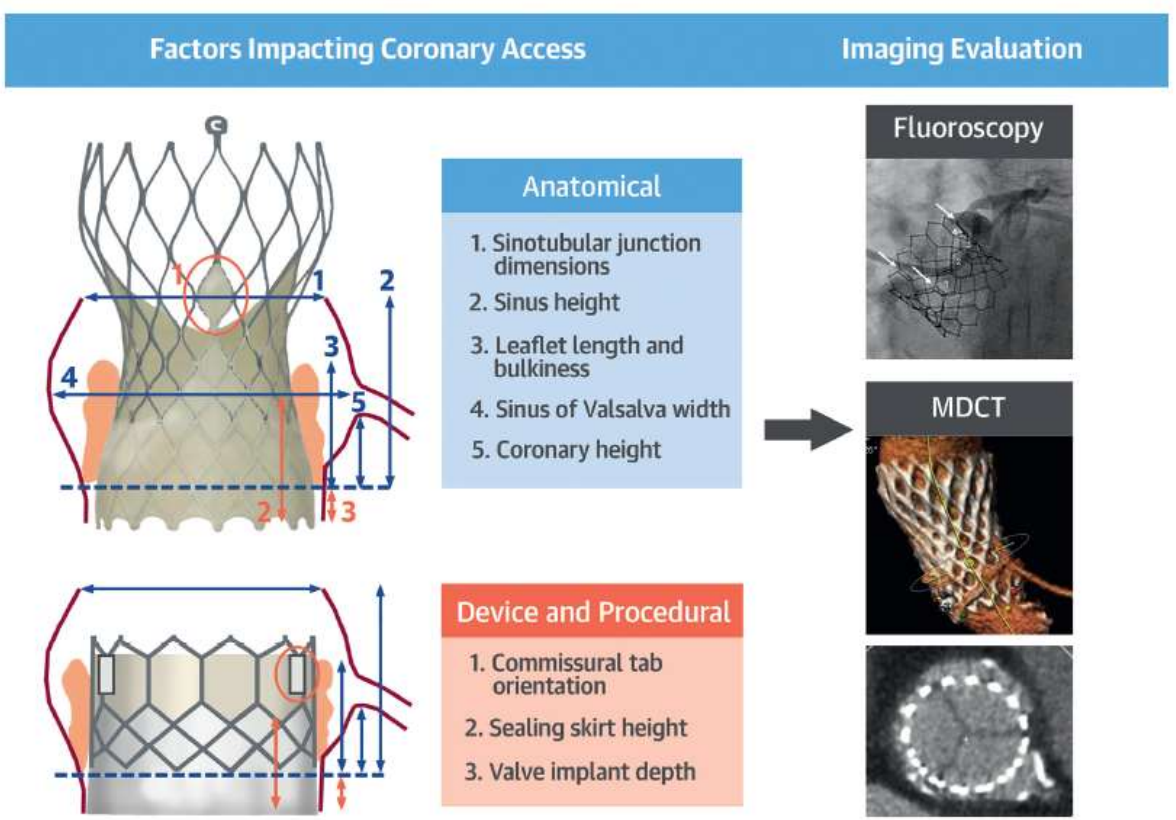


Surgically explanted Sapien and CorveValve THVs

Coronary Angiography and Percutaneous Coronary Intervention After Transcatheter Aortic Valve Replacement

Matias B. Yudi, MBBS,[a] Samin K. Sharma, MD,[a] Gilbert H.L. Tang, MD, MSc, MBA,[b] Annapoorna Kini, MD[a]

CENTRAL ILLUSTRATION Coronary Reaccess After TAVR



Yudi, M.B. et al. J Am Coll Cardiol. 2018;71(12):1360-78.

TAVR Adjunct Pharmacology

Customized Patient-Based Therapy

BEFORE	DURING	AFTER
Acetylsalicylic acid (ASA)	UNFRACTIONATED HEPARIN: target ACT ≥300”	ASA + CLOPIDOGREL
	Bivalirudin: BRAVO (BivalRudin and Aortic Valve intervention Outcomes)	Acetylsalicylic acid (ASA) ARTE trial
	Low Molecular Weight Heparin	Non anti-VKA Oral Anticoagulant ± ASA: Atlantis, Action, GALILEO

TAVR Landscape - 2018

Key Messages

- There are also many 'gaps' in TAVR knowledge which must be addressed (e.g. valve leaflet abnormalities, late TAVR SVD/durability, coronary access considerations, and optimal adjunctive pharmacotherapy).
- By all meaningful criteria, TAVR has been a BREAKTHROUGH Technology!

Celebration of 50th Anniversary of AS Natural History Manuscript

Aortic Stenosis

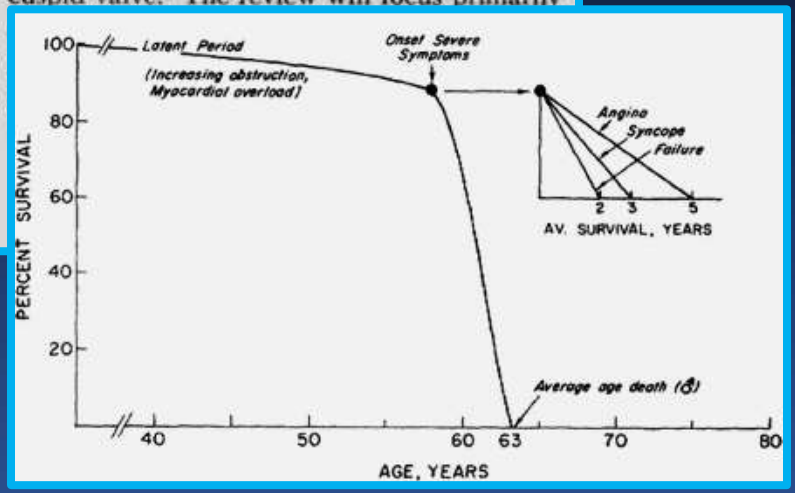
By JOHN ROSS, JR., M.D. AND EUGENE BRAUNWALD, M.D.

THE ADVENT of corrective operations for various forms of heart disease has placed increasing emphasis upon the need for accurate information concerning the natural history of patients with potentially correctible lesions. An understanding of the natural course assumes particular importance in the case of aortic stenosis because of the significant incidence of sudden death associated with this disease and the grave prognosis that appears to accompany the onset of certain symptoms,

patients with isolated valvular aortic stenosis of rheumatic etiology and patients without a history of rheumatic fever who have isolated calcific aortic stenosis; many of the latter patients are now considered to have developed calcification and stenosis of a congenitally bicuspid valve.[1] The review will focus primarily

From the Cardiology Branch, National Heart Institute, Bethesda, Maryland.

Supplement V to Circulation, Vols. XXXVII and XXXVIII, July 1968



Ross and Braunwald, Circulation 1968;38:V-61

Celebration of 50th Anniversary of AS Natural History Manuscript

Ross and Braunwald, Circulation 1968;38:V-61

The Patients are Simply AMAZING!

Patient #1

92 yo man with critical AS…
TAVI at CUMC on 2/8/06…
Playing golf in Palm Springs on 3/8/06!!!

It's is All About the Patients!

Remember,
your patients are
the point-of-care!!!